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STUDIES IN HYPERSENSITIVENESS OF THE MUCOUS MEMBRANE

V. COMPARATIVE STUDIES OF SKIN AND OPHTHALMIC REACTIONS IN HAY FEVER PATIENTS PRESENTING CONSTITUTIONAL REACTIONS

HYMAN SHERMAN, M.D., AND BESSIE BARON, B.A.
BROOKLYN, N. Y.

THE purpose of this investigation was to determine whether there existed in treated hay fever patients who tended to develop constitutional reactions an abnormal degree of reactivity in either the cutaneous or mucosal shock tissues.

There were selected for study forty treated subjects in whom the constitutional reactions were not the result of technical error, accident, or unusual dosage according to skin titrations (Table I). Nineteen patients (47.5 per cent) presented symptoms involving only the mucous membranes of the nose and bronchial tree; nine subjects (22.5 per cent) manifested symptoms of the cutaneous type, i.e., urticaria or pruritus, and nine (22.5 per cent) presented both cutaneous and mucous membrane symptoms. One case experienced repeated attacks of vertigo. Two cases were unclassified. Sixteen of the above forty cases manifested repeated reactions. Of these, seven patients sustained two reactions, four had three reactions, three had four reactions, one had five, and one manifested six reactions. All had a progressive diminution in tolerance to dosage, some having repeated constitutional reactions the same year and others in successive years. A control group of twenty-four cases that developed no constitutional reactions from pollen treatment was also studied. All cases had received preseasonal therapy from one to twelve years.

TECHNIQUE

The conjunctiva was used for studying mucosal reactivity, since it offered obvious advantages over other mucous membranes for purposes

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of investigation. Patients with congestion, inflammation, or inequality in vascularity of the conjunctivae were excluded from this study. All skin titrations and ophthalmic tests were performed in the spring prior to instituting therapy; or during the winter between pollen seasons. Titrations were usually completed at one sitting. In order to minimize variations in technique, one of the authors did all the skin titrations and the other did the ophthalmic titrations.

TABLE I

ANALYSIS OF CASES PRESENTING CONSTITUTIONAL REACTIONS

	TOTAL NUMBER OF CASES	NUMBER OF CONSTITUTIONAL REACTIONS			TYPE OF SYMPTOMS			
		FOUR OR MORE	THREE	TWO	MUCOSAL	CUTANEOUS	MIXED	MISC.
Single Reactions	24				11 46%	5 21%	6 25%	2 8%
Multiple Reactions	16	5	4	7	8 50%	4 25%	3 19%	1 6%
Totals	40				19	9	9	3
Per cent of Total Cases					47.5%	22.5%	22.5%	7.5%

Cutaneous tests were performed intracutaneously on the lateral surface of the arm, employing 0.02 c.c. of pollen extracts containing 0.0001, 0.001, 0.01, and 0.1 mg. N/c.c. Reactions were recorded as slight, moderate, marked, and marked plus, depending upon the degree of the response obtained with the intracutaneous tests. Intermediate degrees of reactivity were also recorded.

Patients who gave a marked reaction to the 0.001 dilution were graded in Class A; those with a marked reaction to 0.001 in Class B; those with a marked reaction to the 0.01 dilution in Class C; those with a marked reaction to the 0.1 dilution in Class D. Those who showed less than a marked reaction to the 0.1 dilution were put in Class E.

On the basis of previous experience with conjunctival titrations, one drop of a pollen extract containing 0.01 mg. N/c.c. was instilled into the conjunctival sac of one eye. A standard 1 c.c. testing syringe, without a needle, was used for this purpose. With the initial ophthalmic reactions and with the cutaneous titrations as guides, the untreated eye was then tested with a weaker (0.001 mg. N/c.c.) or stronger (0.1 mg. N/c.c.) pollen extract as the occasion demanded. It was thus possible in almost all instances to elicit at one sitting sufficient representative ophthalmic reactions to serve as a basis for comparison with the cutaneous reactions. This technique rendered it unnecessary to retest eyes on the same day, a practice which in conjunctival titration is open to criticism. It also obviated the necessity for comparative studies at long intervals, which is also subject to many pitfalls. When retests were needed, an interval of at least seven days was allowed to elapse between tests on the same eye.

Ophthalmic reactions usually occurred in ten minutes and consisted of injection and occasionally edema of the caruncle, limbus, and ocular and palpebral conjunctivae. Depending upon the degree of injection of these tissues, the conjunctival reactions were graded as 1 plus, 2 plus, 3 plus, and 4 plus. After considerable practice, it was possible to distinguish intermediate reactions. For the sake of establishing a working basis for comparison, these grades of reactivity in the conjunctivae were arbitrarily considered to be equivalent to corresponding reactions obtained with intracutaneous titration. To simplify the comparison of cutaneous and conjunctival titrations, the numerical value of 4 was applied to slight cutaneous and 1 plus conjunctival reactions; the value of 8 to moderate cutaneous and 2 plus conjunctival reactions; of 12 to marked cutaneous and 3 plus conjunctival reactions; and of 16 to marked plus cutaneous and 4 plus conjunctival reactions.

TABLE II

CLASSIFICATION OF CASES

DEGREE OF SENSITIZATION BY SKIN TITRATION	NUMBER OF CASES	A MARKED TO 0.0001 MG. N PER C.C.	B MARKED TO 0.001 MG. N PER C.C.	C MARKED TO 0.01 MG. N PER C.C.	D MARKED TO 0.1 MG. N PER C.C.	E LESS THAN MARKED TO 0.1 MG. PER C.C.
Multiple Constitutionals	16	0	3 18.7%	10 62.5%	3 18.7%	0
Single Constitutionals	24	0	6 25%	12 50%	4 17%	2 8%
No Constitutionals	24	0	3 12.5%	12 50%	9 37.5%	0

FINDINGS

In analyzing the group of forty with constitutional reactions from the point of view of skin sensitivity (Table II), it will be noted that among the subjects who had repeated constitutional reactions, three (18.7 per cent) titrated as Class B, ten (62.5 per cent) as Class C, and three (18.7 per cent) as Class D. Among the remaining twenty-four cases, six (25 per cent) were in Class B, twelve (50 per cent) in Class C, four (17 per cent) in Class D, and two (8 per cent) in Class E. There happened to be no Class A cases in this entire group. Among the twenty-four control cases studied, three (12.5 per cent) were in Class B, twelve (50 per cent) in Class C, and nine (37.5 per cent) in Class D. On comparing the relative degrees of cutaneous sensitivity of the constitutional and control groups of cases, it was evident that the constitutional group revealed the greater degree of cutaneous reactivity.

The patients in the constitutional group of cases were treated from one to twelve years. The average period of treatment for the cases giving multiple constitutional reactions was 5.2 years, and for the single constitutional cases 4.6 years. The control group of cases was treated over a period of one to eleven years, the average being four years.

It had been found by previous observers that in the average pollen-sensitive case the skin reacted by the intracutaneous technique to a dilution at least ten to a hundred times weaker than that needed to elicit an ophthalmic reaction by the instillation of the same extracts.[1] This had also been our experience in previous studies. With this fact in mind, comparative titrations were made of the cutaneous and conjunctival reactions in all members of the constitutional and control groups of cases. When the ratio of cutaneous to conjunctival sensitivity exceeded 10:1, the relationship of these tissue sensitivities was considered to be normal. When the ratio was found to be reduced to 10:1 or to less than 10:1, an abnormal relationship could be said to exist. This reduced ratio could be interpreted as indicating either an increased sensitivity of the conjunctiva or a diminished sensitivity of the skin.

TABLE III

EXAMPLES OF COMPARATIVE TITRATIONS OF SKIN AND CONJUNCTIVA

TYPE OF CASE	CASE	SKIN TITRATIONS MG. N/C.C.				EYE TITRATIONS MG. N/C.C.				RATIO SKIN/ CONJUNC.
		0.0001	0.001	0.01	0.1	0.0001	0.001	0.01	0.01	
Const. Reaction	A. B.		6	9		2	8	12		Less than 10:1
	S. G.	4	4	12			8	16		Less than 10:1
No Const. Reaction	E. S.	2	3	12				0	4	Greater than 10:1
	R. F.	2	5	10				0	4	Greater than 10:1
NUMERICAL EVALUATION OF REACTIONS	SKIN REACTIONS				neg. 0	slight 4		mod. 8	mkd. 12	mkd.++++ 16
	CONJ. REACTIONS				neg. 0	1+ 4		2+ 8	3+ 12	4+ 16

The manner in which ophthalmic and cutaneous titrations were compared is illustrated in Table III. After having recorded the numerical evaluation of the ophthalmic and cutaneous reactions, the numerical value of the 0.0001 skin reaction was compared to the value of the 0.001 eye reaction and similarly the value of the 0.001 skin reaction to that of the 0.01 eye reaction, etc. As demonstrated in the case S. G., the value of the 0.0001 skin reaction, four, was less than that of the 0.001 eye reaction which was eight; and the value of the 0.001 skin reaction, four, was likewise shown to be less than the 0.01 eye reaction, 16. Normally, these values bear a ratio of 10:1 or over. In this case, however, the comparative numerical values indicated that the ratio of cutaneous to conjunctival sensitivity was less than 10:1; in fact, less than 1:1. In the control cases E. S. and R.F., a comparison of the numerical values revealed that the ratio of sensitivity exceeded 10:1 and approached the ratio of 100:1 in each case.

Of the twenty-four patients presenting single constitutional reactions (Protocol 1 and Table IV), twelve (50 per cent) revealed conjunctival titrations with ratios of 10:1 or less than 10:1. Of the sixteen patients manifesting multiple constitutional reactions, the ratio of skin to con-

junctival sensitivity was 10:1 or less in eight cases (50 per cent). This made a total of twenty (50 per cent) of the entire group of forty constitutional cases in which there was a reduced ratio of sensitivity. Twenty subjects (50 per cent) showed cutaneous titrations having a ratio greater than 10:1, revealing a normal relationship of sensitivity of skin and conjunctiva. In the control group of twenty-four patients who presented no constitutional reactions following pollen treatment (Protocol 2), four cases (17 per cent) showed a ratio of 10:1 or less than 10:1, and twenty cases (83 per cent) revealed a ratio greater than 10:1. Thus in only 17 per cent of the control cases could there be said to exist a reduced ratio of sensitivity as compared to an average of 50 per cent for the entire group of constitutional cases.

TABLE IV

RATIO OF SENSITIVITY AMONG CASES WITH SINGLE AND MULTIPLE CONSTITUTIONAL REACTIONS

	TOTAL	CASES SHOWING RATIO OVER 10:1 (NORMAL)		CASES SHOWING RATIO 10:1 OR LESS THAN 10:1*	
		NUMBER	PER CENT	NUMBER	PER CENT
Single	24	12	50	12	50
Repeated	16	8	50	8	50
Totals	40	20	50	20	50
Normal Controls (No Constit.)	24	20	83	4	17

*Relatively greater conjunctival reactivity.

DISCUSSION

In analyzing the constitutional cases from the point of view of skin reactivity, it was of interest to note that there were no Class A cases among the group. This may be explained by the fact that in this type of case extremely conservative dosage was given, and therefore no constitutional reactions were seen. Moreover Class A cases formed a relatively small percentage of the cases treated in the clinic.

The authors have used the term "reduced ratio of sensitivity" when the ratio of skin and conjunctival sensitivity was found to be 10:1 or less than 10:1. This reduction in ratio was interpreted as indicative of an abnormal relationship in the degrees of sensitivity of the skin and conjunctivae. The skin test of the average pollen-sensitive individual is twenty to a hundred times more sensitive than the conjunctival test with the same extract. Without the aid of further studies one cannot definitely state whether we are dealing with a state of excessive conjunctival reactivity or a state of diminished cutaneous reactivity where a reduced ratio of sensitivity exists. The former state, however, appears more likely since, as shown in Table II, the constitutional group of cases did not reveal a diminished reactivity of the skin. In fact, a greater cutaneous reactivity was evident in this group of cases, as compared with the control group. The duration of

PROTOCOL 1

TITRATIONS OF CUTANEOUS AND OPHTHALMIC REACTIONS IN CASES PRESENTING CONSTITUTIONAL REACTIONS FROM POLLEN THERAPY

CASE NO.	NO. OF YEARS TREATED	NO. OF REACTIONS	POLLEN DOSES PRECIPITATING REACTIONS (MG. N/C.C.)	TYPE OF REACTIONS	SKIN TITRATIONS				EYE TITRATIONS				RATIO OF SKIN TO CONJ. SENSITIVITY
					0.0001 MG. N/C.C.	0.001 MG. N/C.C.	0.01 MG. N/C.C.	0.1 MG. N/C.C.	0.0001 MG. N/C.C.	0.001 MG. N/C.C.	0.01 MG. N/C.C.	0.1 MG. N/C.C.	
1.	4	1	R.03	Mixed	3	6	9				2	8	Greater than 10:1
2.	5	1	R.05	Generalized Pruritis	3	5	12			3	5	12	10:1
3.	4	3	R.04; R.0275; R.0175	Mucosal	4	6	12			0	2	10	Greater than 10:1
4.	5	1	R.08	Weakness	1	4	6	10			2	10	Less than 10:1
5.	4	1	T.015	Mixed	0	9	12			2	8		Less than 10:1
6.	3	1	T.015	Mixed	3	12				2	4		Greater than 10:1
7.	7	2	R.08	Mucosal	3	9					2	6	Greater than 10:1
8.	3	1	R.025	Mucosal		6	12				4	8	Greater than 10:1
9.	1	2	R.05; R.03	Mucosal	4	5	9			4	16		Less than 10:1
10.	3	3	R.006	Mixed	3	6	9		2	8	12		Less than 10:1
11.	2	2	R.008; R.0015	Mucosal	1	5	10				4	12	10:1
12.	6	1	R.03	Mucosal	1	2	10				2	2	Greater than 10:1
13.	5	2	R.0125; R.01	Mucosal		5	8	12			2	10	10:1
14.	4	4	R.025; R.01; R.009; R.007	Cutaneous	1	6	8	10		2	6	12	Less than 10:1
15.	3	1	R.001	Mucosal	4	5	12			8	16		Less than 10:1
16.	8	1	R.04	Cutaneous		6	6	6			4	8	10:1
17.	12	2	R.007; R.004	Cutaneous		5	12			0	6	12	10:1
18.	8	1	R.025	Cutaneous		5	5	12			2	6	Greater than 10:1

19.	6	2	R.035; R.002	Mixed	3	4	9				2	8	Greater than 10:1
20.	6	1	R.01	Mucosal	5	12				4	12		10:1
21.	6	2	R.015; R.015	Cutaneous	4	4	10				2	12	Greater than 10:1
22.	4	1	R.015	Mucosal	3	6	10			1	8		10:1
23.	2	1	R.015	Mucosal	4	5	12				4	14	10:1
24.	9	3	R.01; R.002;	Mucosal	4	7	12			2	6		Greater than 10:1
25.	3	1	R.0015 R.07	Mucosal	2	3	12					2	Greater than 10:1
26.	8	1	R.015	Mixed	4	10				2	6		Greater than 10:1
27.	6	1	R.02	Mucosal	3	5	10				5	10	10:1
28.	7	1	R.1	Mixed	5	10				5	10		10:1
29.	9	4	R.04; R.002; R.01; R.02	Mucosal	8	12				0	6		Greater than 10:1
30.	1	1	R.006	Cutaneous	3	12			0	3			10:1
31.	3	1	R.009	Cutaneous	5	12				2	4		Greater than 10:1
32.	3	1	R.01	Mucosal	4	10			0	4			10:1
33.	8	4	R.004; R.003; R.002; R.0008	Vertigo	4	6	10			4	10		Less than 10:1
34.	1	1	R.001	Mixed	4	6	12			1	6		Greater than 10:1
35.	2	3	R.0003; R.0002	Cutaneous	2	4	10			1	10		Greater than 10:1
36.	2	1	R.035	Mucosal	2	4	12				2		Greater than 10:1
37.	1	5	R.015 to R.005	Mixed	2	6	10				1	6	Greater than 10:1
38.	10	1	R.004	Cutaneous		6	12				1	2	Greater than 10:1
39.	6	1	R.03	Mucosal	3	6	6	12			1		Greater than 10:1
40.	4	6	R.025 to R.005	Mixed	5	12			1	6	10		10:1

NUMERICAL EVALUATION OF REACTIONS

SKIN REACTIONS: neg. 0; slight 4; mod. 8; mkd. 12; mkd.++++ 16

CONJ. REACTIONS: neg. 0; 1+ 4; 2+ 8; 3+ 12; 4+ 12

R=Ragweed Extract
T=Timothy Extract

PROTOCOL 2

TITRATIONS OF CUTANEOUS AND OPHTHALMIC REACTIONS IN CASES ACCEPTING POLLEN THERAPY WITHOUT CONSTITUTIONAL REACTIONS

CASE NO.	NO. OF YEARS TREATED	HIGHEST DOSE MG. N/C.C.	SKIN TITRATIONS				EYE TITRATIONS				RATIO OF SKIN TO CONJ. SENSITIVITY
			0.0001 MG. N/C.C.	0.001 MG. N/C.C.	0.01 MG. N/C.C.	0.1 MG. N/C.C.	0.0001 MG. N/C.C.	0.001 MG. N/C.C.	0.01 MG. N/C.C.	0.1 MG. N/C.C.	
1.	5	R.09	2	4	6	9		2	6	12	Less than 10:1
2.	5	R.05	2	4	10				4	12	Less than 10:1
3.	2	R.03	2	4	12				2	8	Greater than 10:1
4.	3	R.05	2	3	12				0	4	Greater than 10:1
5.	6	R.09		3	4	12			2	4	Greater than 10:1
6.	3	R.07	5	10				2	12		Greater than 10:1
7.	0	----	2	4	6	12			2	6	Greater than 10:1
8.	11	R.08	3	4	5	13		2	5	12	10:1
9.	1	R.01	2	5	10			0	0	4	Greater than 10:1
10.	3	R.015	4	6	12			0	6	12	Greater than 10:1
11.	2	R.01	1	3	5	12			6	10	Less than 10:1
12.	2	R.05	2	3	12					6	Greater than 10:1
13.	4	R.045	2	5	12				2	8	Greater than 10:1
14.	0	----	3	5	5	10				4	Greater than 10:1
15.	1	T.05	0	2	5	10				0	Greater than 10:1
16.	3	R.0175	3	5	10			2	4		Greater than 10:1
17.	2	R.03	2	5	10				2	8	Greater than 10:1
18.	4	R.03	3	4	12				2	4	Greater than 10:1
19.	0	----	2	8	12				2	4	Greater than 10:1
20.	7	R.05	5	12				2	8		Greater than 10:1
21.	9	R.1	1	4	7	9		0	4	6	Greater than 10:1
22.	8	R.09	3	6	10	14		0	4		Greater than 10:1
23.	2	R.04	3	10				0	4		Greater than 10:1
24.	10	R.03	2	4	6	10			1	4	Greater than 10:1

SKIN REACTIONS	neg. 0	slight 4	mod. 8	mkd. 12	mkd.++++ 16
CONJ. REACTIONS	neg. 0	1 + 4	2 + 8	3 + 12	4 + 16

treatment was not a factor influencing the results obtained, the average being four years in the control group and 4.8 years for the entire group of constitutional cases.

There appeared to be no uniform relationship between the type of constitutional reaction experienced by the patient and the degree of his cutaneous or conjunctival reactivity (Table V). Among the nineteen cases manifesting mucosal symptoms, nine (22.5 per cent) showed a relatively normal ratio of sensitivity of skin to conjunctiva. Of the nine patients presenting reactions of the cutaneous type, four (10 per cent) revealed a reduced ratio of sensitivity of skin to conjunctiva. Four subjects (10 per cent) revealed a skin reactivity of 100:1 or more. Of these, three had mucosal symptoms and one had cutaneous symptoms. However, in the nonconstitutional group of cases, three (12.5 per cent) revealed a similar degree of high skin reactivity.

TABLE V

RATIO OF SENSITIVITY AMONG DIFFERENT TYPES OF CONSTITUTIONAL REACTIONS

TYPE OF CONSTITUTIONAL REACTION	CASES SHOWING RATIO GREATER THAN 10:1 (NORMAL)		CASES SHOWING RATIO OF 10:1 OR LESS (RELATIVELY GREATER MUCOUS MEMBRANE REACTIVITY)		TOTALS
	NUMBER	PER CENT	NUMBER	PER CENT	
Mucosal	9	22.5	10	25	19
Cutaneous	5	12.5	4	10	9
Mixed	6	15	3	7.5	9
Unclassified	1	2.5	2	5	3
Totals	21	52.5	19	47.5	40

The writers have described a technique with which it is possible to compare conjunctival and cutaneous sensitivity in hay fever patients. It is not to be inferred, however, that with this technique one can detect all cases that may be subject to constitutional reactions. Furthermore, it remains to be seen by future studies whether such a technique will prove to be of practical value in the prevention of constitutional reactions in the treatment of pollen-sensitive cases.

SUMMARY

1. Forty treated cases of hay fever that developed constitutional reactions which were not the result of technical error, accident, or unusual dosage were studied. Comparative titrations of skin and conjunctival reactivity by a special technique revealed that a total of 50 per cent of these cases showed a reduced ratio of skin and conjunctival sensitivity.

2. Of the sixteen cases that manifested repeated generalized reactions, 50 per cent revealed a reduced ratio.

3. In a control group of twenty-four treated patients who developed no constitutional reactions, only 17 per cent showed a reduction in the ratio of sensitivity.

4. As no evidence was disclosed to indicate that a diminished cutaneous reactivity was present in the constitutional group of cases, it seems likely that the reduced ratio was a result of an excessive hypersensitivity of the mucous membranes in these cases.

REFERENCE

1. Fineman, A. H.: Studies in Hypersensitiveness No. 13: A Comparative Study of the Intradermal, Scratch, and Conjunctival Tests in Determining the Degree of Pollen Sensitivity, J. Immunol. **11**: 465, 1926.

DISCUSSION*

DR. MATTHEW WALZER.—In discussions of constitutional reactions occurring in hay fever patients receiving conservative dosage, there is a tendency to focus attention upon antibodies of one kind or another as the responsible factor. A high reagin concentration, the presence of heterophile antibody, and absence of the thermostabile antibody represent some of the explanations which have been offered for these reactions. Although some of these factors undoubtedly are involved, too little attention has been given to the shock tissue factor in such phenomena. By showing that the ophthalmic mucous membranes in patients with repeated constitutional reactions tend to manifest a degree of reactivity which is abnormally high when compared to cutaneous sensitivity in the same patients, Sherman and Baron again stress the importance of the role of the shock tissue in allergic phenomena.

The authors have devised a crude technique for comparative titrations of the ophthalmic and cutaneous sensitivities in the same patient, but they are not prepared to offer this as a practical procedure for ophthalmic titration and for the prevention of constitutional reactions. Ophthalmic titrations are subject to many more technical limitations than are cutaneous titrations. One great handicap is that only two conjunctivae are available in each patient for titration, and good technique does not permit retests of these surfaces at frequent intervals. Sherman and Feldman have shown that conjunctival responses may be altered for variable periods of time following ophthalmic reactions caused by allergic excitants (pollens, danders, etc.) or by nonspecific (histamine, dionin, etc.) substances. Under the circumstances, a quantitative technique which is based upon repeated testing of the ophthalmic or other mucous membranes, at short intervals, is subject to considerable error. This situation is not unlike that which obtains in the skin when retests of the same cutaneous site are made at frequent intervals.

*This discussion was attached by error to the article "Hypersensitiveness of the Mucous Membrane, IV," by Sherman and Feldman which appeared in the last issue of the Journal.

ARTHUS TYPE OF SENSITIVITY TO LIVER EXTRACT

SAMUEL E. RYNES, M.D., AND LEANDRO M. TOCANTINS, M.D.
PHILADELPHIA, PA.

HYPERSENSITIVITY to liver extract is being reported in medical literature with increasing frequency. In 1940 Harten and Walzer[1] comprehensively reviewed this subject and noted only twenty-eight cases of proved allergic reactions to liver extract, exclusive of histamine-like and nonspecific febrile reactions. One year later Taylor and Hilger were able to collect six additional cases of liver allergy from the literature and to add two more of their own.[2] During the past two years, twelve more examples of this type of allergy have been described.[3-6] Eight of these cases have come from a single clinic.[3] Thus, a total of at least forty-eight cases have been reported up to the present time.

The sensitization phenomena in almost all of the reported cases have consisted of urticaria, asthma, severe gastrointestinal disturbances, and collapse reactions of anaphylactic nature. Such manifestations have occurred either singly or in combination. In only a few instances have reactions of an inflammatory nature been mentioned. Harten and Walzer cite four cases of severe local inflammation or edema following intracutaneous tests of large volume (0.1 c.c.). Castle and Minot have encountered indurated reactions with secondary infection, which have required surgical drainage and which they felt might be due to allergy.[7] Murphy has twice observed the production of hematomas at the site of liver extract injections.[8]

The majority of the forty-eight reported cases of liver extract sensitivity appear to be of the acquired type. Intradermal or scratch tests with commercial liver extract preparations have shown positive reactions in most of the patients who developed allergic reactions following one or more therapeutic injections of this material. Many have also shown positive passive transfer tests to these extracts, indicating the presence of reagins. Precipitins were present in three of the five cases in which they were sought.[2, 3, 9] Only six of the forty-eight patients had positive skin reactions to whole liver extracts (Coca solution), and four of these had some other previous manifestation of allergy.[3, 9, 10, 11] The presence of skin reactions to the homologous muscle proteins occurred in but two of these forty-eight cases.[2, 12] One of these two gave a history of allergy to ingested beef, for which the skin test was positive.

These observations support Criep's conclusion that the acquired type of liver sensitivity is primarily due to organic and not biologic specificity.[9] Feinberg, Alt, and Young[3] agree that the antigen is not species-

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specific and further state that "it is specific as a special organ fraction bound up with the antianemic fraction." However, the possible existence of a naturally occurring sensitivity of a biologic type must be considered, inasmuch as two of the patients showed skin reactions to the homologous muscle proteins and one showed skin reactions to homologous kidney and stomach extracts. Furthermore, in one case it was possible to control the symptoms by changing to an extract of a different animal source.[3]

Fig. 1.—Intradermal tests on patient.

Medial Row	*Lateral Row*
Pork muscle	Pork liver
Beef muscle	Beef liver
Lamb muscle	Lamb liver
Chicken muscle	Chicken liver

The following case exhibits the less common form of liver extract hypersensitivity; namely, that characterized by severe localized inflammatory responses or an Arthus type of reaction.

The patient, a white woman aged 40, the wife of a physician, was first seen in August, 1942, with an anemia which had begun during a pregnancy in 1935 and which recently had shown rapid progression. A diagnosis of pernicious anemia was made and confirmed by the blood findings (hemoglobin 57.4 per cent; R.B.C. 2,010,000; W.B.C. 3,150), the absence of free HCl in the gastric contents, burning sensation of the tongue, megaloblastic transformation of the bone marrow, and such

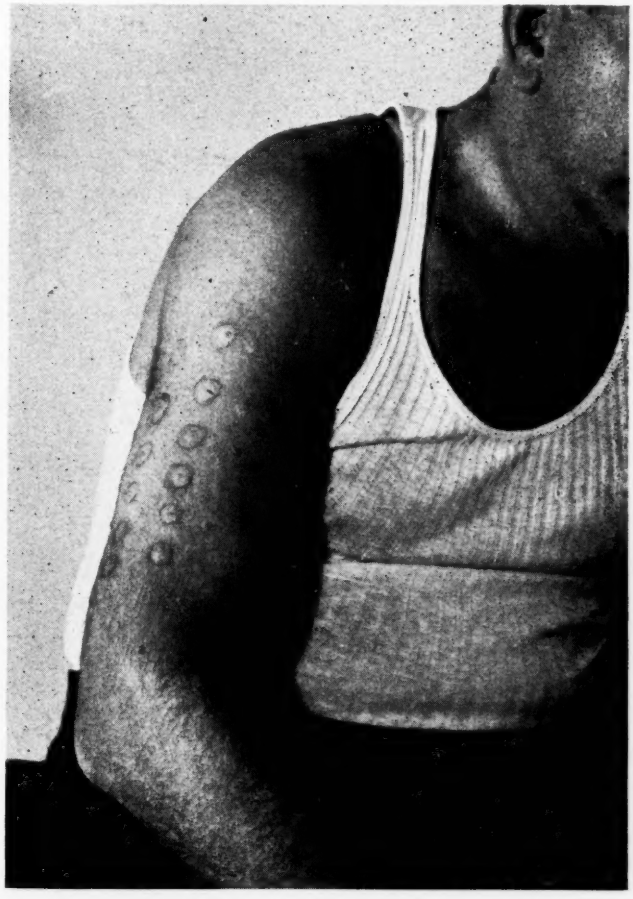

Fig. 2.—Passive transfer tests. (Passive transfer sites are indicated by the rings.)

Beef liver (whole)
Pork liver (whole)
Chicken liver (whole)
Lamb liver (whole)
Veal liver (whole)
Pork muscle

neurologic symptoms as numbness and tingling in the extremities. Her past medical history showed occasional mild bouts of urticaria and some intermittent nasal blockage. Her son suffers from nasal and bronchial allergy. Physical examination was not remarkable except for the smooth atrophic tongue so commonly found in pernicious anemia patients.

In 1937 she received for the first time an intramuscular injection of liver extract (Lilly) in the left buttock. This produced, at the site of the injection, a severe inflammatory reaction which began within twenty-four hours and reached its height ten days later. An incision

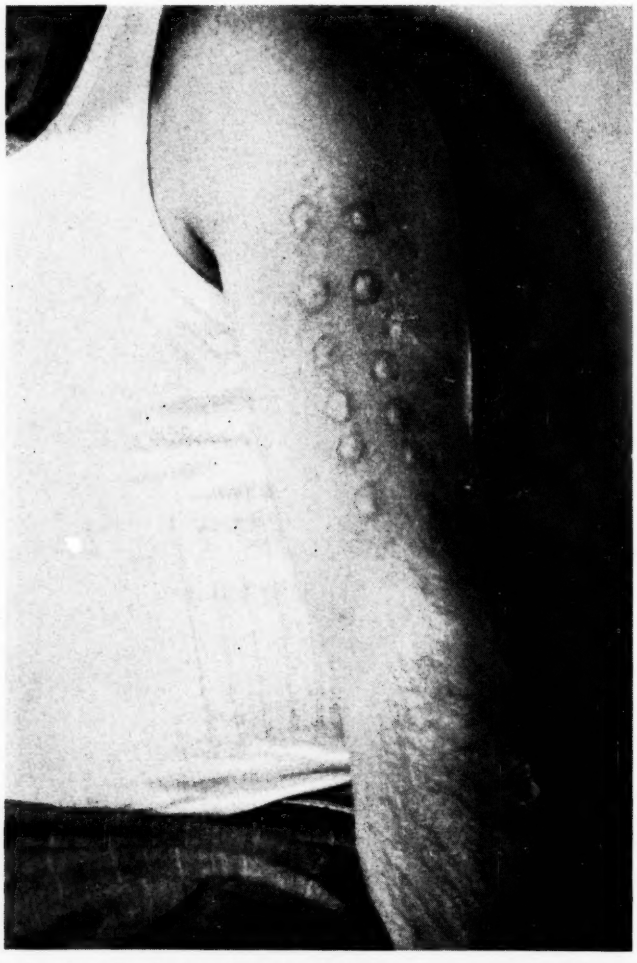

Fig. 3.—Passive transfer tests. (Passive transfer sites are indicated by the rings.)

Medial Row	*Lateral Row*
Lederle 5U. (1-10)	Abbott Pork (1-100)
Pork and beef	
Lilly Pork (1-10)	Lilly Pork (1-100)
Wilson Beef (1-10)	Beef liver (1-100)
Beef liver (1-10)	Pork liver (1-100)
Pork liver (1-10)	Beef muscle (1-100)
Lamb liver (1-10)	Pork muscle (1-100)

was made under general anesthesia, and drainage continued for about two months after surgical intervention. A staphylococcus was cultured from the abscess, but the specimen of liver extract from which the injection had been made was found to be bacteriologically sterile. Six months later 0.5 c.c. of reticulogen was injected into the right deltoid

muscle. Within twelve hours, severe pain developed, along with an edematous reaction of such intensity that the arm was swollen to approximately twice its normal size. This reaction persisted for ten days. In May, 1942, an intradermal injection of 0.1 c.c. of liver extract from another source (Upjohn) produced edema so intense that the skin ruptured spontaneously and the arm had to be carried in a sling for two weeks. The ingestion of ventriculin (pork stomach, Parke-Davis) and lextron (iron and pork liver, Lilly) caused nausea, vomiting, and abdominal pain; bepron (beef liver and iron, Wyeth), however, was tolerated. The patient was able to eat cooked calf, beef, and lamb liver without trouble. The ingestion of pork liverwurst caused nausea, but goose liverwurst produced no untoward symptoms.

TABLE I

REACTIONS TO ANTIANEMIC LIVER EXTRACTS

COMMERCIAL ANTIANEMIC LIVER EXTRACTS	DIRECT SKIN TESTS (INTRADERMAL AND SCRATCH)	INDIRECT TESTS (PASSIVE TRANSFER)	
		1942	1943
Abbott (Pork)	3+ (1-100,000)	2+	2+ (1-10,000)
Lilly (Pork)	3+ (1-10,000)		2+ (1-10,000)
Rorer	2+	+	
Lederle (Pork and Beef) (5 units)	2+	+	0
Squibb (Beef)	+ (1-10,000)	±	±
Wilson (Beef)	+	0	0
"Lex" (Beef)	+	±	
Lederle (Beef) (15 units)	+ (1-10,000)	0	±
Winthrop	+	+	
Harvey (Horse?)	+	0	+

Figures in parentheses indicate the highest dilution producing a positive reaction.

Direct skin tests by the scratch and intradermal methods produced very definitely positive reactions to ten commercial liver extract preparations and to five different whole liver extracts in Coca's solution. Strong reactions were also shown to pork, beef, and lamb muscle extracts. Frequently, delayed reactions of indurated character followed the intradermal tests to commercial pork liver extract, whole pork liver, and pork muscle extracts. These lasted from twenty-four hours to five days. No similar reaction occurred at the site of any other animal liver or muscle extract test. Passive transfer tests showed the presence of reagins which corresponded to all the whole liver and muscle antigen reactions. Reagins were also definitely present to the commercial pork liver extracts. However, the passive transfer tests for the commercial beef liver extracts were not consistently positive. All of the strongly positive passive transfer reactions which had been obtained in 1942

were again obtained one year later. Some of the reactions are shown in the accompanying illustrations. The results of these tests are summarized in Tables I, II, and III. (In many instances it was difficult to determine the biologic source of the commercial liver extracts, since this was stated on the label by only one manufacturer.) No precipitins to the commercial or whole liver extracts were obtained by the ring test.

Other positive intradermal skin tests shown by the patient included house dust, feathers, cotton seed, milk, egg, coffee, horse serum (1:1000 marked), and horse dander. The history of personal and family allergy and the large number of positive skin reactions obtained by intradermal tests, particularly the strongly positive horse serum test without any previous serum therapy, are indicative of a naturally occurring sensitization to animal tissues in an allergic individual.

TABLE II

REACTIONS TO AQUEOUS WHOLE LIVER EXTRACTS

WHOLE LIVER EXTRACTS (COCA SOLUTION)	DIRECT SKIN TESTS (INTRADERMAL AND SCRATCH)	INDIRECT TESTS (PASSIVE TRANSFER)	
		1942	1943
Pork	3+	2+	2+ (1-100)
Beef	2+	2+	2+ (1-100)
Veal	+	2+	+
Lamb	3+	+	+
Chicken	+	+	+

TABLE III

REACTIONS TO MEAT ANTIGENS

MUSCLE PROTEIN EXTRACTS (COCA SOLUTION)	DIRECT SKIN TESTS (INTRADERMAL AND SCRATCH)	INDIRECT TESTS (PASSIVE TRANSFER)	
		1942	1943
Pork	2+	+	+ (1-100)
Beef	+	+	+ (1-100)
Lamb	2+	+	+
Chicken	±		

The fact that both the antianemic fraction and whole pork liver extracts produced greater immediate and delayed reactions with intradermal skin tests plus the fact that the ingestion of pork liver and stomach caused vomiting seemed to indicate a biologically specific type of sensitivity. It was, therefore, decided that an attempt should be made to develop a tolerance to a commercial beef liver extract. This was successfully accomplished in eight injections when a dose of 1 c.c. (15 units) was reached. During the period of hyposensitization, several slight local reactions occurred. Thereafter, the dose was increased to the point where a total weekly dose of 6 c.c. could be administered and

tolerated. Despite the tremendous amount of liver given, the hematologic response was slow and unsatisfactory. A two-month period was required to raise the hemoglobin from 57 to 75 per cent and the red blood cells from 2,010,000 to 3,400,000. The peak of reticulocyte response was only 2.6 per cent in contrast to the 10 to 15 per cent response which is usually seen. The red blood cell count reached a level of 4,000,000 only after a period of five months' intensive treatment, but this count was not maintained. It was then felt that because of the sensitivity of the patient's tissues, there might be some destructive effect on the antianemic substance and that the large doses might be enhancing this effect. Therefore, the weekly dose was gradually reduced to 1 c.c. with little significant effect on the blood count. The most recent blood count, made on Nov. 2, 1943, was 70 per cent hemoglobin and 3,300,000 red blood cells per cu. mm.

SUMMARY

1. A patient who apparently represents a naturally occurring sensitivity to animal tissues with biologic specificity is reported. This differs from the usual type of hypersensitivity to liver extract which has been described in the literature as being of the acquired variety.

2. The injections of commercial liver extract known to be derived from pork liver caused severe reactions of the Arthus type on two occasions. Other manifestations of localized tissue allergy occurred in the gastrointestinal tract when the ingestion of pork liver or stomach produced severe abdominal pain and vomiting.

3. It is supposed that some similar reactions in the hematopoietic system may be responsible for an incomplete response to ordinarily adequate therapeutic doses of liver extract.

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DISCUSSION

DR. LEO H. CRIEP.—This very interesting paper brings out several points about which one cannot be too dogmatic. I shall consider only three of these and indicate possible points of speculation.

In a patient with an allergy to a biologic product, one must determine whether one is dealing with an organ-specific allergy (i.e. allergy to liver, pancreas, etc.) or with a species-specific allergy, i.e., an allergy to the animal (muscle and serum) from which the liver extract was obtained.

If the sensitivity, let us say in a case of pernicious anemia, is to the protein of liver regardless of biologic source, it stands to reason that the patient is in a bad way, because he will not tolerate liver extract regardless of its source. On the other hand, if the allergy is species-specific, let us say to pork muscle, serum, and liver only, then by simply changing the batch of extract to beef liver extract, treatment may be continued.

Dr. Rynes' patient could not tolerate pork liver by mouth; nor could she tolerate the injections of extracts of pork liver, pork stomach, or beef liver. Passive transfer tests showed good positive reactions (2+ and 3+) to pork and beef liver, but only a slight reaction to lamb liver; the passive transfer reactions to pork and beef muscle were less definite. Before counting a 1+ reaction as significant, one would have to know how much antigen was used in these tests. On the basis of the clinical reactions described above and the findings of reagins against both beef and pork liver and less definitely against beef and pork muscle and serum—on the basis of these facts, one may ask whether the patient under consideration does not exhibit a limited organ—(i.e., liver) sensitivity, rather than a species-specific sensitivity.

Another very valuable clinical point made by the authors is that allergy to liver extract in their patient interfered with its antianemic value. Similar experiences in connection with the occasional lack of therapeutic response to insulin on the part of insulin-allergic diabetic patients have been reported. Cannon explains this interference on the basis of localization of the insulin or liver extract in the tissues and the lack of proper absorption. Or, it may be, that local inflammation destroys or reduces the activity of the biologic product. Just why this interference should occur in some and not in all instances of allergy to biologic products is not clear and certainly not accounted for by the above explanation.

Finally, the authors make another point by concluding that their patient "represents a naturally occurring sensitivity to animal tissue." In support of their contention, they offer considerable evidence both clinical and experimental. One is tempted to ask whether this is really an instance of natural allergy to liver extract or rather an instance of acquired allergy similar to that observed in serum reactions and occurring in a patient who happens also to be atopic. Let us examine the facts. This patient developed an anemia in 1935. The first known injection of liver extract was given in 1937 when she developed a severe local reaction. However, reagins were demonstrated for the first time in 1942 after the patient had received liver therapy. The questions arise therefore: Is it possible that she may have received without knowing or remembering it some liver therapy by mouth or by injection before 1937, the time of the occurrence of the supposed first

injection and reaction so that there was previous exposure? And further, is it possible that the antiliver extract reagins demonstrated to be present in 1942 resulted from previous liver therapy?

What evidence is there that these specific antiliver reagins played any role in mediating the local reaction that followed liver therapy? Tuft and others have reported marked and severe local reactions following the injection of insulin into a patient. One of the two patients reported by me as allergic to liver extract gave marked local reactions following injection of the extract. Such reactions have been shown to occur both in the presence and in the absence of the specifically related reagins. Furthermore, in the case of allergy to pancreatic tissue extract, reagins were still demonstrable in his serum. This would seem to indicate that the mere presence of specific reagins is no proof they play a role in producing the reaction.

The swelling and edema of the buttock in Dr. Rynes' patient started about twenty-four hours following the injection of liver extract and gradually increased in intensity, reaching the peak in ten days. Could this be interpreted as a latent period analogous to that seen in serum reaction rather than the characteristic sudden immediate type of reaction so commonly observed in natural allergy?

The very fact that it was possible to completely desensitize this patient in eight successive injections with liver extract would lend weight against the assumption of the atopic character of this allergy.

The foregoing is intended more to stimulate discussion than disagreement with the authors' findings which are so well authenticated. They should be congratulated for presenting us with the problem of the patient who because of an allergy to a biologic product had difficulty in availing herself of its therapeutic aid.

THE CAUSES OF HAY FEVER OCCURRING BETWEEN THE GRASS AND RAGWEED SEASONS

ROBERT CHOBOT, M.D., AND HAROLD D. DUNDY, M.D.
NEW YORK, N. Y.

DURING the past three years an increasing number of patients in the New York area have complained of hay fever and asthma from the last week of July until Aug. 10. This is an interim period during which grass and ragweed patients should be symptom-free.

These symptoms have usually been ascribed to inhalants such as dust, feathers, and molds (particularly alternaria), or to upper respiratory infections. But distress has been apparent despite the absence of these irritants. The possible presence of other pollens was therefore considered.

Mr. Fred H. Hodgson, the botanist, was consulted. He reported that only four pollens could be suspected in this area: marsh elder, wild rice, corn, and cocklebur. They all pollinate during the period under question.

1. *Marsh Elder (Iva frutescens)*—and its close relative high water shrub, also an Iva. It is found, but not abundantly, along tide water marshes, especially lining drainage canals. The pollen grain closely resembles that of short ragweed; its spines are less prominent; the germinal furrows are very short; the exine is granular.

2. *Cultivated Corn.*—It yields at the end of July a heavy, polygonal or rounded pollen, averaging 95 microns in size. It is usually not wind-pollinated, but it can be.

3. *Wild Rice (Zizania palustria).*—It is a tall grass common in the Hudson River Valley, sometimes reaching the height of 12 feet, growing in the swampy borders of streams or in shallow water. It has been believed to be only slightly distributed.

4. *Cocklebur.*—This has not been considered a menace because of its scanty production. The pollen is very fine and light and resembles giant ragweed. The pollinating period is extremely variable; early in dry soil, later and more abundant in moist. It may start by July 15 and continue through September.

Pollen surveys failed to reveal the presence of these pollens to any extent. But nevertheless, they could not be eliminated as possible offenders, for they are extremely difficult to identify. Marsh elder is only slightly smaller than ragweed, with spines only slightly less prominent; according to many botanists, the two are almost indistinguishable.

From the Pediatric Allergy Clinic, Department of Pediatrics, New York Post-Graduate Medical School and Hospital, Columbia University.

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Cocklebur and wild rice are similarly difficult to differentiate, one from the other, and from ragweed. Only corn presents no problem.

The four pollens were, therefore, chosen for testing and treatment.

Patients were tested with extracts made in the usual manner after defatting with ether, extracted with buffered saline, and standardized on the protein nitrogen basis. All cases were tested with 10, 100, and 1000 units of each extract, with conjunctival tests performed on all patients with marked reactions. Passive transfers were done with 10 sera; seven of the ten sera used transferred and verified the presence of skin-sensitizing antibodies.

TABLE I

PASSIVE TRANSFER REACTIONS WITH SERUM C: CONTAINING ANTIGENS TO RAGWEED, MARSH ELDER, AND COCKLEBUR

SERUM MIXTURE	TESTED WITH	REACTION
1A Serum + Ragweed 20,000	Ragweed 1000	0
B Serum + Ragweed 20,000	Marsh Elder 1000	++
C Serum + Ragweed 20,000	Cocklebur 1000	++
2A Serum + Marsh Elder 16,000	Ragweed 1000	+++
B Serum + Marsh Elder 16,000	Marsh Elder 1000	0
C Serum + Marsh Elder 16,000	Cocklebur 1000	++
3A Serum + Cocklebur 14,000	Ragweed 1000	++
B Serum + Cocklebur 14,000	Marsh Elder 1000	++
C Serum + Cocklebur 14,000	Cocklebur 1000	0

Neutralizations were done with four sera, as outlined by Cooke. These were patients with positive skin and eye tests to several of the pollens under study. The sera were mixed with equal parts of the various pollen extracts and incubated overnight in the icebox. Intradermal sites were injected, each containing 0.1 c.c. of the mixtures, and, after 48 hours, were tested with the respective antigens. The immunologic specificity of these antigens was demonstrated, as for example in Table I. Similarly, neutralization and cross-neutralization occurred in the other three sera, with wild rice in one, marsh elder in the second, and corn and cocklebur in the third. As shown by Sherman and Stull,[2] neutralization is very frequent; reciprocal cross-neutralization between closely related antigens is also quite common.

Two hundred and fifty cases of ragweed hay fever were studied to determine the incidence of preseasonal symptoms. Forty-five or 18 per cent complained of symptoms before the onset of the ragweed season. These 45, together with 75 patients with hay fever without preseasonal symptoms, were observed for clinical appraisal.

Of the 45 cases with preseasonal symptoms, direct skin testing revealed 11 marked and 18 moderate reactions, totaling 29, or 64 per cent to marsh elder; 10 marked, and 18 moderate, totaling 28 or 62 per cent to wild rice; 11 marked, and 15 moderate, totaling 26 or 58 per cent to cocklebur; and 9 marked, and 11 moderate, totaling 20 or 44 per cent to corn. There were 13 marked reactions, or 29 per cent to Alternaria.

Of the 75 cases of ragweed hay fever with no preseasonal symptoms, there were 57 or 76 per cent with moderate and marked reactions to marsh elder; 57 or 76 per cent with moderate or marked reactions to cocklebur; 47 or 63 per cent to wild rice, and 41 or 58 per cent to corn. There were 7 or 9 per cent with marked reactions to Alternaria. It is obvious that there is no significant difference between the two groups.

Ninety-three unselected cases were put into one group for intensive observation and study. Of these, 15 finally remained to warrant treatment with one or more of these pollens. They were treated for a period of two seasons with results ranging from satisfactory to excellent in all cases. The average dose required was not large, never exceeding 5000 protein nitrogen units.

TABLE II

SKIN REACTIONS IN 45 CASES WITH PRESEASONAL SYMPTOMS

	MARKED	MODERATE	TOTAL	PER CENT
Cocklebur	11	15	26	58
Corn	9	11	20	44
Marsh Elder	11	18	29	64
Wild Rice	10	18	28	62
Alternaria	13		13	29

TABLE III

SKIN REACTIONS IN 75 CASES WITHOUT PRESEASONAL SYMPTOMS

	MARKED	MODERATE	TOTAL	PER CENT
Cocklebur	17	40	57	76
Corn	8	33	41	55
Marsh Elder	13	44	57	76
Wild Rice	11	36	47	63
Alternaria	7		7	9

DISCUSSION

The presence of a positive skin test to any or all of these pollens does not justify immediate treatment. For example, the majority of ragweed hay fever cases with symptoms strictly limited to the ragweed season show marked reactions on skin tests to timothy, or plantain, or to both. This does not, of course, warrant the inclusion of timothy and plantain extracts in the treatment of a ragweed hay fever case. The presence of other etiologic possibilities must be considered. Upper respiratory infections often mimic the symptoms of hay fever and must be excluded as a causative factor. The molds, particularly Alternaria, reach their peak by the end of July and must be differentiated from this group under discussion. Inhalants, such as cat or dog dander or feathers must be evaluated. Hence, the combination of positive skin tests, clinical observation for at least one season, followed by treatment during the following season with critical evaluation of the results obtained, seems to us the only satisfactory method of approach to this type of problem.

The results of this program of diagnosis and treatment suggest that these pollens may no longer be disregarded in the New York area; that they *are* present in the atmosphere; and they are in sufficient concentration to affect a significant number of patients.

We make no claim for the discovery of the cause of a new group of hay fever cases. Marsh elder is well known as the most important single cause of hay fever in some areas of the country. Cocklebur too is frequently considered a factor.

As has been shown by Prince and Secrest,[3] the inclusion of marsh elder extract in the therapy of ragweed patients exposed to marsh elder produced satisfactory results. They confirmed that marsh elder contains an allergen not present in giant, western, or common ragweed. Similarly, Grubb and Vaughan[4] have shown that when several pollens in a group react positively, it is sometimes necessary to hyposensitize with more than one of the positive reactors. Closely related pollens from the same botanical family show evidence of the existence of group-specific and species-specific allergens. No single pollen of any group could be considered representative of the entire group.

To conclude, the pollens under discussion are now troublesome in the New York area, and for some poorly understood reason are becoming increasingly so. It seems necessary, therefore, that a patient exhibiting preseasonal symptoms be suspected of sensitivity to any or all of these pollens, and that he be observed for at least one season under a program of testing with exclusion of other causative factors. The persistence of unexplained symptoms during this period indicates clearly the need for the inclusion of any or all of these pollen extracts in treatment.

SUMMARY

1. The immunologic specificity of marsh elder, wild rice, and cocklebur has been shown.

2. Skin tests are no index for treatment, except after observation.

3. Treatment relieves symptoms.

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DISCUSSION

Dr. Albert Vander Veer.—I want to congratulate Dr. Chobot on his excellent presentation of a most interesting subject which I am sure will eventually prove as important as the work on plantain by Bernton and others some twenty years ago. Most of us in the East have been missing

a bet by considering ragweed the only important cause of hay fever after the middle of July. I think we were led to this belief by the reports of our botanists that other pollens which caused so much trouble in the West and South were too scanty here in the East to be of any importance. We ascribed the reason for our comparatively poor results in the treatment of late hay fever to the enormous amount of ragweed pollen in the air. The fact that many of our patients began to have hay fever before there was any ragweed pollen in the air led Dr. Chobot and others to extend their investigations to other possible causal weeds with the results shown in his paper. I thoroughly agree with him that the mere presence of positive skin tests does not necessarily call for treatment. We usually treat any case of late hay fever beginning in August with ragweed alone for the first season. If the result is poor, we add other pollens to which the patient gives positive tests. Dr. Chobot is correct when he says that relatively small doses are required to give protection to the less prevalent pollens, and it is often possible to use mixtures containing one-half to two-thirds ragweed extract, and the other one-half or one-third is made up of three or four fall pollens to which the patient reacts.

To Dr. Chobot's list I would like to add three other weeds which I believe are often causal factors, namely amaranth, Artemesia, and chenopod, all of which can be found in this area, although, of course, not nearly so abundant as ragweed. These, too, are apt to begin pollinating before ragweed.

I would like to present one case history which I believe illustrates the possible importance of *Artemesia vulgaris* or mugwort.

Case 1.—A male patient, aged 42, was first seen June 1, 1915. He gave a history of late hay fever which began in Minnesota in 1901, and symptoms occurred from Aug. 15 to Oct. 15 or later. He gave a marked reaction to ragweed and a negative to golden rod and yarrow. He was treated with heavy doses of ragweed (equivalent to 30,000 protein units) perennially through 1915 and 1916 with only slight relief.

He went to Canada during the hay fever season from 1917 to 1927 and was all right there.

From 1927 through 1938 he was treated with heavy doses of ragweed, and while he was usually free in New York (where he worked), he always had trouble when he returned to his home in Mount Vernon. During these years he was frequently tested with other fall pollens, as amaranth, chenopod, cocklebur, and iva, to which he gave moderate reactions, and they were added to his ragweed in varying amounts up to 1,500 units each. The result was always unsatisfactory. He was negative to molds.

In 1939 he was first tested with artemesia to which he gave a marked reaction, more than to ragweed. He was treated with ragweed, 20,000 units, and a combination of chenopod, cocklebur, mugwort, and sage (both the latter being artemesias), 10,000 units, and had no hay fever even in Mount Vernon.

A similar combination was used in 1940 and 1941 with equally good results. In 1942 he decided to go without treatment and had severe hay fever both in New York and in Mount Vernon from mid-August to early October. In 1943 he again gave a marked reaction to mugwort (artemesia) with moderate reactions to ragweed, amaranth, chenopod, cocklebur, and iva. He was treated with ragweed to 24,000 units, and the rest in combination up to 2,500 each. He spent all summer in Mount

Vernon and had 80 per cent relief with only two bad days, Sept. 11 and 20.

I admit that if we want to absolutely prove this case, it would be necessary to send a botanist to Mount Vernon and find a large patch of artemesia near his house, but this would be expensive, and next year we should treat him only with ragweed and artemesia. I am sure the patient prefers to stick to the mixture which has carried him through in past years.

Two other artemesia patients occur to my mind, both of whom told me they were exposed to artemesia. They gave marked skin reactions to it and were greatly helped when it was added to their mixtures, although in one case the total dose of each of the fall pollens was about 200 units; this substantiates Dr. Chobot's remarks that if the right mixture is chosen, it may not require heavy doses to obtain a good result. One of these patients came from North Carolina and the other from Michigan, so you can see how impossible it is to make exhaustive pollen surveys in all cases.

CONTACT DERMATITIS RESULTING FROM THE MANUFACTURE OF SYNTHETIC RESINS AND METHODS OF CONTROL

STEPHEN D. LOCKEY, B.S., M.D., F.A.C.A., LANCASTER, PA.

THE principal synthetic resins manufactured in the United States are:

1. Phenol-formaldehyde resins sold under various trade names, such as, Bakelite, Durite, Durez, Resinox, Indur, and Catalin.

2. Urea-formaldehyde resins, sold under trade names, such as Beetle and Plaskon.

3. Coumarone resin made from coal tar residue.

4. Ester gums which are natural resins, such as, rosin, dammar, copal, in which the acid of the resin has been combined with glycerol.

5. The glyptal resins, which are a combination of glycerol and an organic acid, such as, phthalic and malleic acids.

6. The vinyl resins, which are vinyl esters, ethers, or halides combined with phenol, formaldehyde, and hexamethylenetetramine.

7. Furfural resins obtained from combining furfural with phenol and formaldehyde. (Furfural is obtained from corn cobs by treating with H_2SO_4 and by fractional distillation.) Also there are those made from soy beans and corn kernels.

8. Chlorinated resins obtained by chlorinating various oils and balsams.

These resins are used for many purposes, as follows:

1. For making plastics, such as, push buttons, pipe stems, cigar holders, bottle caps, airplane parts, buttons, ornaments, telephone receivers, plates for artificial teeth, finger nail polish, fabric coating finishes, household utensils, and automobile parts.

2. For making varnishes, flexible coatings, and floor finishings.

3. For making cements, wall boards, gears, dishes, water containers, and rubber compounds.

Over 2600 various objects used in this country are made of resins. The most important of these, from the standpoint of volume manufacture and skin hazards involved, are the phenol-formaldehyde and the urea-formaldehyde resin.

PHENOL-FORMALDEHYDE RESINS

These are made in two principal varieties. They are: (1) the cast resin which is finished in the factory, and (2) the molding resin which is sold to molding companies and completed in the molding process.

Formaldehyde and ammonia are mixed in proper proportions in a kettle with either phenol, cresol, dimethyl-orthocresol, or paratertiaryamyl phenol and heated a sufficient length of time and to the

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proper temperature. After combination takes place, they are drawn out of the kettle in the form of a syrup. This is run into pans and allowed to cool, when it solidifies. This is known as first-state resin or alpha resin. The pans are then heated; the resin is remelted and poured into suitable molds. These are placed in large mineral oil-filled carriers and put in curing ovens, where they are heated and where they go through the so-called beta and gamma stages into the completed cast resin.

After being taken out of the oven, the molds are removed from the oil, the resin is removed from the molds, and the oil is washed off with soap and water and dried. It is then ready to be carved, lathed, or bored into whatever object is desired.

During the course of these operations, formaldehyde is given off, and the air of the room is strong with the odor of it unless adequate forced ventilation is employed. Workers in the room who are sensitive to formaldehyde may develop dermatitis of the face, neck, and arms, as well as of the covered parts where there is friction, such as the belt line, the angle at the shoe top, and the wrist at the cuff line.

The oil used in the curing process dissolves out of the resin some of the phenols and formaldehyde; if the oil is used over and over again without purification, it can contain considerable quantities of these substances. One sample which was analyzed after it came out of the ovens contained 2 per cent each of phenol and formaldehyde. The men handling this oil have their clothes splashed with it and at times suffer not only from oil acne and dermatitis of the legs, thighs, and other parts touched by the oil-soaked clothing, but also from dermatitis due to the irritating action of the phenol and formaldehyde. The eruption in these cases is usually a diffuse erythematous base on which there are scattered the papules and pustules of an oil folliculitis.

The girls who wash the oil off the resin with soap and water may also develop dermatitis of the hands and arms from the oil, and, also, from the strong soap solution with which their hands are constantly wet. In many factories the oil is treated with sodium hydrate after each baking in order to neutralize the phenol and formaldehyde it may contain; but if this is not carefully done, dermatitis may result from too much alkali in the oil.

The skin hazards to the users of these cast resins are practically nil, since no phenol or formaldehyde is given off from the finished product.

The molding resin is made up in numerous qualities, containing different proportions of phenol, formaldehyde, and ammonia. It is carried to the alpha state or beta stage and then is ground, heated, and mixed with ground wood, zinc stearate, soap, dyes, and hexamethylenetetramine in a mix mill. From this mill it is discharged on to conveyers where it is air-cooled. While cooling, it forms lumps which are ground in mills to proper sizes fit for molding. The workers engaged in mixing, grinding, and packing the molding resin are all exposed to the dust

of the irritating chemicals it contains as well as to the formaldehyde which it gives off, the odor of which permeates the rooms. Dermatitis is a frequent occurrence among workers in these occupations, especially if the rooms are not properly ventilated to draw off dust and if the machines where there are dust and fumes are not properly ventilated by suction-ventilating hoods.

In one factory employing about 400 workers where no great care was taken to allay and prevent dust, 27 cases of dermatitis occurred in eight months. Patch tests performed on ten patients with various types of the resin (hexa, 4 per cent solution of formaldehyde, and 2 per cent solution of phenol) showed that hypersensitivity to hexamethylenetetramine and to formaldehyde was the cause of 80 per cent of the occupational dermatitis in this plant. Hypersensitivity to phenol was also found, but in lesser degree than to formaldehyde and hexa.

The actual cause of dermatitis from exposure to hexa and formaldehyde is the same. They both finally decompose in the presence of warmth and moisture into formic acid, which is the real skin irritant.

The dermatitis from the dust of the molding resins usually occurs at the points of friction with the clothing: the wrist, belt line, inguinal area, shoe tops, collar line, and post auricular area, especially if the worker wears glasses. It may, however, occur on the covered parts when the dust penetrates or permeates the clothing. The skin of the face and around the eyelids may also be affected. The eruption usually consists of scattered papules and vesicles on an erythematous base. It clears up if the worker stays away from work and returns again if he resumes work.

In this factory the dermatitis was more prevalent in the winter because the workers did not change clothes or take showers after their shift in cold weather, whereas, in summer they were more likely to do so.

UREA-FORMALDEHYDE RESINS

These are made by mixing urea and formaldehyde. No heat is required, the reaction generating its own heat. A syrupy liquid results. This is mixed with bleached sulfite pulp under heat and pressure and dried in tray dryers. It is then mixed in a ball mill with pigments, zinc stearate, and a small amount of hexamethylenetetramine, about 0.5 per cent. It is then screened and is ready for shipment. Minute amounts (fraction of 1 per cent) of other ingredients are added to different brands of urea-formaldehyde resins.

The manufacture of the urea-formaldehyde resins on a commercial scale is more recent than that of the phenol-formaldehyde resins; hence, the two factories where these resins were made had more modern machinery and safety appliances than the phenol-formaldehyde resin factories. There were adequate ventilation facilities and good facilities for dust prevention. As a result, among 190 employees there had occurred only four cases of dermatitis over a period of more than two

years. They were due to hypersensitivity to formaldehyde. Two chemists in the experimental laboratory of these plants were hypersensitive to formaldehyde and suffered with dermatitis when exposed to it. One of them could expose his forearm to the mouth of an open bottle of formalin, and almost immediately an erythma would develop on the exposed skin.

In a molding plant in Ohio employing about 300 workers, where phenol-formaldehyde and urea-formaldehyde resins are used, twenty-six cases of dermatitis occurred in the first ten months of 1934, and in a molding plant in Pennsylvania one-half of the workers developed dermatitis in the hot months of 1935.

The process of molding is practically the same for all resins. The powder is placed in a "pill machine" and pressed into proper shape for the molds. The pills are then put into the molds where they are subjected to heat and pressure which shapes and hardens them. During the molding process gases are given off from the molds and the odor of formaldehyde is strong in the room, irritating the nose, throat, and eyes of those unaccustomed to it.

There is an excess of powder in the molds which flows out during the molding process and is only partially "cured." This is called the "flash." When the molds are opened, the "flash" is cleaned off the molds and filed off the molded object.

Patch tests with the resins with which they worked were performed in the winter on two workers with active cases of dermatitis, and on ten workers who had previously had dermatitis. Only two positive reactions resulted, both on the active cases, one to the phenol-formaldehyde resin and one to the urea-formaldehyde resin. The examination and history of the ten workers who had had dermatitis but were free from it when the patch tests were made showed that two had dermatophytosis and one probably had pityriasis rosea. It is probable that a considerable number of the twenty-six cases reported in 1934 were not of industrial origin.

The same plant was revisited in August, 1935. Twelve cases of dermatitis had occurred since the first visit nine months before. This time nine workers who had dermatitis were tested with seven suspected samples of urea-formaldehyde and phenol-formaldehyde resins, as well as with hexamethylenetetramine. Four showed no reactions after twenty-four hours to any of the seven patches applied. Five showed positive reactions to one or more of the resins, and of these five, three showed positive reactions to hexamethylenetetramine.

Two of the four who showed no reaction had eruptions at the time the patches were applied. One was a case of dermatophytosis, and the other was an eczema which dated back to childhood. The weather was cold (less than 70°) during the period the patches were on, and this may have a bearing on the reactions, because, of the twenty-six cases

reported in 1934, eighteen had occurred during periods of hot weather in May, June, July, and August.

There can be little doubt that a considerable percentage of dermatitis in this plant was of occupational origin.

That hexamethylenetetramine is a major causative factor is indicated by the fact that most of the cases occurred in workers handling the phenol-formaldehyde resin, which contains many times more of the hexamethylenetetramine than does the urea-formaldehyde resin.

Hexa, which was extensively used in the rubber industry as an accelerator and caused many cases of dermatitis, has now been almost entirely displaced by other accelerators. It is a necessary ingredient in certain phenol-formaldehyde and ammonia required to go through the gamma stage, or to completion.

In the urea-formaldehyde resin, hexa acts as a stabilizer to prevent the resin from hardening before it is molded. Less than 1 per cent of it issued in the resin.

The ventilating and dust prevention conditions in the molding plants were poor. There were no suction hoods over the molding machines. The suction hoods over the "pill machines" were out of order. The workrooms were only ventilated by windows, and wash-ups or showers after work were not compulsory. With proper dust allaying facilities, such as forced ventilation, suction hoods, wet sweeping of floors after each shift, compulsory showers, protective clothing, and ointments, the incidence of dermatitis in these plants could be decreased.

Dermatitis may occur in users of molded phenol-formaldehyde and urea-formaldehyde resin wares if the hexa is not all combined. Theoretically it is all combined in the completed resin, but practically, as in some imperfectly cured pieces in which there is too much hexa in the molding compound to be completely taken up, there may be a sufficient amount remaining to cause dermatitis in hypersensitive people. The same thing may be true of the phenol if not completely combined.

PREVENTIVE MEASURES FOR THE PROTECTION OF WORKERS AGAINST SKIN HAZARDS FROM SYNTHETIC RESINS AND WAXES

Each employee should have a complete physical examination.

1. In order to show that a dermatitis is caused by occupational substances, it must be established: (1) that the dermatitis followed contact with the resin. (2) that the portion of the skin which came in contact with the resin was first affected, and (3) that hypersensitivity to the resins is or was present as shown by the fact that a powdered portion of the suspected substance placed on the clear skin near the eruption in the form of a patch test gives a positive reaction if left on from twenty-four to ninety-six hours.

To determine the actual chemical in the resin which caused the dermatitis, the nature and chemical composition of the resin must be

determined and patch tests performed on the patient with each of the chemicals composing it.

The patches of the chemical should be in such dilutions that will not cause reaction on the normal skin if left on for twenty-four hours. A 2 per cent aqueous solution of phenol can remain on the normal skin in the form of a patch test for twenty-four hours without causing a reaction. A 4 per cent solution of formaldehyde can remain on the normal skin in the form of a patch test for twenty-four hours without causing a reaction. Powdered coumarone resin may remain on the normal skin, in the form of a patch test, for twenty-four hours without causing a reaction.

2. The allergic background of each employee should be very carefully investigated. If his ancestors were allergic he should not be employed in this department. New applicants for jobs should have a complete physical examination and be carefully scrutinized for skin diseases, and those found to have them should not be employed. About 43 per cent of employees who claim compensation for contact dermatitis have their claim disproved. Trichophytosis, eczema, and other skin lesions are often found. It is, therefore, equally important to disprove as well as prove a case of contact dermatitis. There sholud be periodic medical examinations of workers to detect cases of dermatitis.

3. Clean working clothes consisting of long sleeves or long-sleeved overalls fastened at neck and wrists should be provided. The clothes should be cleaned daily and should not constrict the worker in any manner, as dermatitis often develops at the site of constriction.

4. Facilities should be furnished to each worker so that he can change from his street clothes to his working clothes. The lockers for street clothes and work clothes should be in separate rooms with the shower baths between the locker rooms. The worker coming in to work enters the locker room used for the street clothes, takes them off and puts them in the locker, and goes into the locker room where his clean work clothes are kept and dons them. From this room he goes to the workroom through a connecting door. At the end of his shift he goes through this door to the work clothes locker room, takes off his work clothes, and leaves them there to be washed, and then goes to the street clothes locker room, puts on his street clothes, and goes out of the door leading to the street. It has been estimated at one plant where such a system was instituted that 9 cents a day per worker will take care of furnishing clean work clothes each day. Employees should never be allowed to wear their working clothes home, as this extends the time of exposure.

Where synthetic waxes are used or made, eating should be prohibited in the workrooms. Suitable eating places should be provided and the workers compelled to wash the hands and clean under the nails before eating.

5. The workrooms themselves should be ventilated by intake exhaust fans to remove dust and fumes. The floors, walls, ceilings, and machines

should be washed down or vacuum-cleaned at frequent intervals to keep them fresh and free from dust and wax.

Dispensers containing 70 per cent alcohol can be set up in the manufacturing area. Alcohol neutralizes phenol and formaldehyde when present on the skin. During warm months frequent washing of the forearms acts as a preventive measure.

6. Workers, who have abrasions or skin breaks, should be treated immediately as dermatitis often starts at the site of an abrasion.

SUMMARY

1. The composition of the principal synthetic resins manufactured in the United States and their chief uses have been stated.

2. The process of manufacture of phenol-formaldehyde and urea-formaldehyde resins which account for many cases of contact dermatitis have been described.

3. Preventive measures have been pointed out.

DISCUSSION

DR. MARION SULZBERGER.—It is surely unnecessary to detail once more the general protective and other measures to be taken to prevent dermatitis among workers in plants manufacturing artificial resins. These measures have been set forth explicitly and at length not only by Dr. Lockey, but also in the general directives, articles, and texts dealing with Industrial Dermatoses; for example, the publications of Louis Schwartz and associates. However, it may be interesting to this audience to hear of the causes of contact dermatitis due to artificial resins as encountered in dermatologic practice, both private and clinic. The multitude and variety of consumer articles which are made from plastics and artificial resins is great and ever-increasing, and almost all have been reported to cause sensitization and contact dermatitis. Thus, in our practice, Dr. Rudolf L. Baer and I have in recent years seen cases due to the following articles:

1. Clothing finishes (shorts, stockings, shirts, pajamas, etc.)
2. Nail lacquers
3. Hair lacquers (pads)
4. Lacquers on feathers, hats, etc.
5. Lacquers on hair pins
6. Wrist watch straps, garter straps, and belts
7. Bottle caps
8. Buttons
9. Artificial jewelry of various kinds, spectacle frames, etc.
10. Steering wheels
11. Earpieces (of hearing devices, radio receivers, etc.)
12. False dentures (plates)
13. Instruments (physicians', dentists', etc.)
14. Toys and lacquered objects used in games
15. Toilet seat and other paint and furniture lacquers

This list, which I have compiled from memory, is surely not complete, but will suffice to show the widespread and diverse opportunities for contact with artificial resins. In most of our cases the sensitivity

was directed to a formaldehyde type of resin; and often the patients gave reactions to patch tests, not only to the original articles, but also to 5 per cent dilutions of formalin. This makes it necessary in such cases to consider also other common sources of exposure to formalin; including medicaments (hexamethylene tetramine); antiperspirants, etc.; sterilizing procedures for cabinets, gloves, and instruments; paper towels, tissues, and toilet papers; disinfectants used in shoes; pathologists' fixing solutions, and rubber "accelerators."

There are two points in which the clinical observations and skin tests throw light on Dr. Lockey's remarks. The first point is that even the finished plastic articles often emanate or give into solution at the skin surface sufficient resin or formaldehyde to cause severe dermatitis in persons strongly hypersensitive.

The second point is that in artificial resin dermatitis the hypersensitivity is often but not always directed to formalin, is sometimes directed to other fractions of the resin, such as gum esters; but is, as far as I know, never directed to formic acid. This latter is a direct irritant, but is not, as far as I can discover, an allergen, and is not directly concerned in the production of the eruption in any of our very numerous cases of contact-type dermatitis due to artificial resins.

THE DISPOSITION OF SOLDIERS WITH BRONCHIAL ASTHMA*

PERCY JONES GENERAL HOSPITAL, BATTLE CREEK, MICHIGAN

MAJOR RALPH I. ALFORD,† M.C., A. U. S.

IN establishing criteria for the disposition of patients with bronchial asthma, in Army hospitals, the present concepts of allergy must be taken into consideration. Cornerstone clinical principles of allergic conditions were laid down in the decades between the two World Wars. On this knowledge have been built practical applications to allergic problems today. By correlating this knowledge with the experience gained so far in this war, we may formulate certain policies and reach more definite conclusions. Earlier concepts have been discarded, and we are no longer confused by the germ theories of Von Helmholtz, the passive immunity theory of Dunbar, or the numerous surgical procedures in vogue at the beginning of the century. Since 1900, there has come a better understanding of anaphylaxis, acquired and inherited states of hypersensitivity, antibody formation, skin sensitivity, and the influence of environment. Specific methods of hyposensitization have found a widespread application in this period. It was only in 1910 that Auer reported the observation that anaphylaxis in guinea pigs resembled the bronchial spasm of asthma. In 1911 Noon reported success in treatment by producing active hyposensitization with specific antigens. This new era opened barely five years before the first World War and thus did not have time enough to develop and be of benefit to military medicine. Since the first World War, large allergy clinics have been established, graduate medical courses given, allergy societies formed, text books written, two allergy magazines published, and boards for the certification of allergists organized. Methods of testing have been improved, and extracts for diagnosis and treatment have been made more specific and effective. Today almost every large Army hospital has an allergy clinic, and extracts are prepared and distributed to other Army hospitals from the Fourth Service Command Laboratory. Allergy is at another crossroads with a tie to the past in the homeopathic principle of treating like with like and a tie to the future with immunology and its important contributions toward the prevention of disease. So far, the application of principles of immunity to clinical medicine has been of untold benefit to mankind. As the knowledge of the mechanisms of immunity unfolds, so in turn will come advances in the treatment of allergic conditions.

The relation of hay fever to asthma is now generally understood and accepted. From 20 to 40 per cent of individuals with untreated hay

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†On leave from New York University Medical School, Allergy Department.

fever develop asthma. Early treatment of hay fever is essential in order to reduce the number of new cases of pollen asthma. It has been estimated that there are over 2,500,000 cases of hay fever in the United States each year. Insurance statistics indicate that there are 500,000 cases of asthma in the United States at all times. In the first World War there were two cases of asthma for every one thousand soldiers, and there were over two men rejected for asthma by the draft boards for every one thousand examined. The number of hospital admissions for asthma also increased markedly during the months of August and September. Few of the selectees with hay fever are turned down today by their induction boards.

A large percentage of them are candidates for asthma in the Army because of unusual exposures of Army life and closer contacts with concentrations of dust, pollens, and molds. Eighteen per cent of the first one hundred cases of asthma at the Percy Jones General Hospital had hay fever before or with their asthma. Soldiers with hay fever should be treated not only in order to be more useful in the spring and summer months, but also so that the number of new cases of asthma may be reduced. The presence of men in the Army with bronchial asthma may at first seem strange and unexplainable. A survey of these men, in reference to their induction, reveals sufficient and good reasons for their admission to the Army. Many men were inducted during a period when they were free from asthma. A medical board will not usually reject a man solely on the basis of a history of asthma when he has no physical signs to confirm it. Certain nonallergic inductees could take advantage of such an opportunity for deferment. Other soldiers were anxious to join the Army and did not reveal their allergic condition. Men with asthma were often accepted because of the pressure exerted on their induction boards to fill up quotas. Medical examiners not infrequently told men that a change of climate would be of benefit or that Army doctors would take care of them. There was often a history of asthma only in childhood, and these men honestly felt that they were cured or had outgrown it. Thus, many allergic inductees have become soldiers, and, sooner or later, most of these men reach the dispensary or hospital. Other men have never had asthma although there is a strong family history of allergy. Contact with new and powerful offending agents often resulted in asthma developing for the first time many miles from the home environment to which they had become accustomed. Men with bronchial asthma have little, if any, place in the army. There is still an effort made to salvage men in order to utilize man power. We must ask, "Will this man be able to remain on duty if returned to service?" The answer to this will usually be "No." The burden of proof rests on the Medical Officer as to why the patient should remain on duty.

In working up a case of allergy we are more dependent on the history than on any other line of investigation. We could sooner dispense with the physical examination, x-ray, laboratory tests, or skin tests. We are

primarily interested in reaching an early decision in order to determine the medical disposition, and the study of the patient's past health record is of inestimable value. We must know what percentage of his time has been spent off duty as a result of his disability. The history of childhood asthma is important, and also whether the present attacks are merely a continuation or a recurrence of it. If the asthma first developed overseas we know that his chances of returning to duty are better than for an asthmatic patient of long standing. The type of duty for which the soldier is qualified must also be considered. A soldier trained for sedentary, inside work will have a better chance for adjustment than one trained for outdoor duty involving exercise and dusty exposures. A patient who has been working at a desk will have a better chance of returning to duty than one trained with combat troops. We must also consider the patient in the light of his own personality and qualities as a soldier. Patients can learn to live and adjust themselves to disabilities and be useful. On the other hand, they may adopt a pattern for failure, leaning on a disability as an excuse for laziness or the avoidance of every unpleasant task. Men who have already assumed this attitude of life can rarely be salvaged for any useful purpose in the Army.

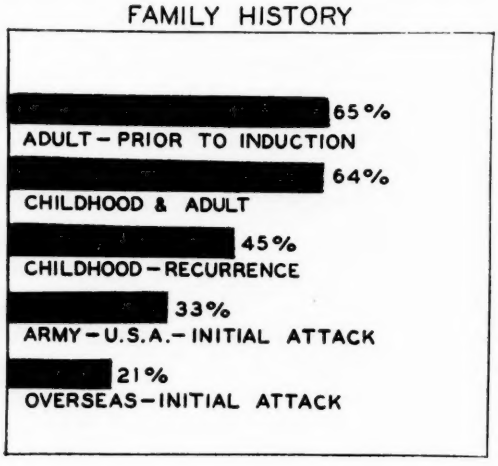

Fig. 1.

The disposition board is frequently handicapped in the ultimate fulfillment of its function by the varied conception of nonstrenuous duty by other officers. One patient on limited duty was doing strenuous exercise as a dock worker unloading ships. Another patient had done well as a cook until he was given commando training. Swimming with a full pack caused a recurrence of asthma which had not given symptoms for two years in Army service. A sergeant, already on limited duty, was assigned in charge of a cleaning detail which was the most dusty work on his post. Great numbers of men could be saved for useful and essential military service if care were taken to fit them in their proper niche.

Our first important problem is to determine how to select men for discharge and how to choose those we plan to keep in the service. A summary of the first hundred cases at Percy Jones General Hospital reveals that 71 per cent were discharged and 29 per cent were returned to limited duty. By far, the greater number discharged were those who had had asthma in childhood which continued on into adult life. Those who had asthma for the first time or who had a recurrence of asthma, long quiescent since childhood, constituted the highest percentage returning to duty. The first group also had a more dominant family history: 59 per cent, as compared with that of the second group, 19 per cent. It is interesting to know that 92 per cent of these patients had never had tests or treatment previous to their induction in the Army. The patients were divided between country and city in regard to their origins in the same proportion as is the general population distribution.

After making any survey of a group of patients and compiling statistics, it is not always easy to arrive at true and logical conclusions. Different interpretations may justly be placed on the same collection of facts. The first hundred cases of bronchial asthma admitted to Percy Jones General Hospital have been studied, and certain information of interest and possibly of value has beeen assembled. These cases represented about 10 per cent of the medical admissions at the time. Inasmuch as this group represents an already selected type of case, it cannot be considered a cross section of the Army. However, it does represent the experience here, and no attempt will be made to bring out all the various interpretations that may be placed upon them. It is for the mutual benefit and guidance of all concerned to learn of the experiences of others. An objective examination will often reveal shortcomings and false impressions which may have a remedy.

In addition to the tests listed on the regular Medical Department Allergy Form 55 E-9, these patients were tested with five additional common molds and seven other mold extracts, secured by culture from moldy leather goods brought back by patients. Dust extracts which were prepared from dust secured from their barracks bags were also used. No comprehensive research program was contemplated or attempted. It should be definitely stated that the first and sole consideration here was the prompt and proper disposition of these patients. There are obvious discrepancies and gaps in the specificity of these extracts when we consider the lapse of time and distance of origin of our material. However, it is interesting to know that attacks of asthma were induced by inhaling the dust of these barracks bags, passive transfers were produced, and one patient had a severe attack of asthma after the injection of 0.1 c.c. of concentrated overseas dust extract. The overseas dust usually produced a larger wheal than our stock U.S.A. dust. It is not customary to make nitrogen determinations on dust, but following these responses this determination was made. It was found that even when using

smaller total amounts of dust material than usual, the nitrogen determination was 20 times as strong as our stock U.S.A. dust. Tests with mold extracts were not conclusive as Table II will show. It may well be that mold extracts prepared overseas would be much more specific than the ones prepared here. These patients always remarked that dust and dampness brought on their attacks. Dampness, alone, may be a trigger mechanism as it lowers body resistance. Apparently the dust is higher in antigenic potency, clinically and also in nitrogen content, than we are accustomed to find in our usual stock dusts. The answer to asthma in the South Pacific probably lies in the factors of dust, molds, and dampness.

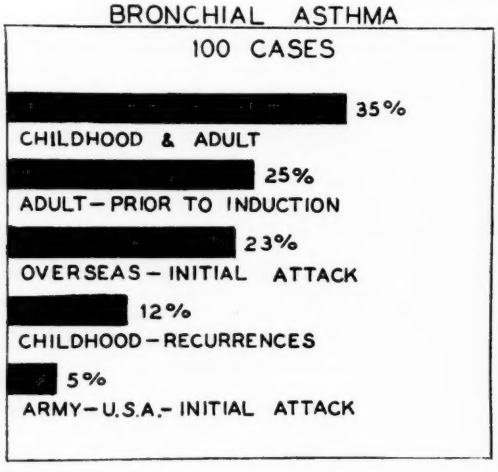

Fig. 2.

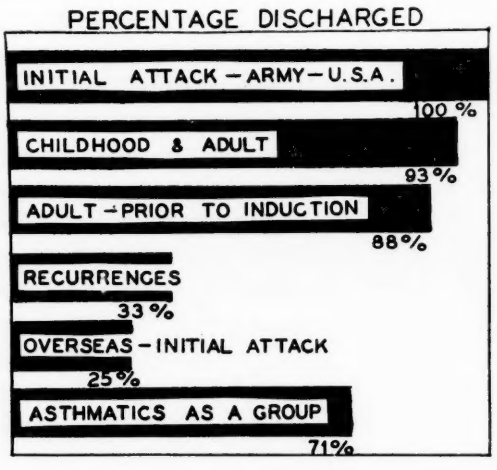

Fig. 3.

In conclusion, we are dealing with intangibles as far as recurrences or aggravation of symptoms is concerned. Probably no other condition in military medicine is so conspicuous by its great number of dispensary visits, confinements to quarters, and repeated hospital admissions. These patients averaged 19 per cent days of disability in proportion to their total days of Army service. They had from 2 to 8 admissions to hospitals before admission to Percy Jones General Hospital for disposition. For this reason, criteria for their disposition cannot be as dogmatic or clear-cut as in other medical conditions. However, by keeping in mind the concepts of allergy as we know them today, we can more accurately deal with cases which otherwise might cause some question. To have principles for guidance will make the task easier, and with a large number of cases the dispositions will have a more uniform and rational basis. Asthma, migraine, and dermatologic allergies are usually incapacitating and render a soldier unfit to perform his duties. These patients should be discharged unless the medical officer can find a good reason for keeping them in the service. The hypersensitive state whether acquired or

TABLE I

AVERAGE DAYS OF DISABILITY

From entrance in Army until admission to Percy Jones General Hospital	35
Percy Jones General Hospital:	
Clinical days	23
Administrative days	11
Total	34
Number of days off duty until disposition at Percy Jones. This represents 19 per cent of total service	69
Limited duty	34
Medical discharge	34

TABLE II

SKIN TESTS

EXTRACTS	PACIFIC ASTHMATICS	U.S.A. ASTHMATICS
Stock dust	83%	96%
Pacific dust	94%	88%
Pollens	4%	15%
Common molds	30%	30%
Pacific molds	40%	35%
Average positive tests to 60 common foods	2.8	4.4

inherited will probably be a potential threat of continued or recurrent disability. It is impossible to give a soldier the same environmental protection against dust, molds, pollens, foods, or dampness that he can have in civilian life. Even for specific therapy carried over many months to be successful, there also must be adequate protection against offending factors in the environment. Patients with chronic bronchitis or asthma should not be sent overseas. Exposures to dust, molds, and dampness will be even greater there than in this country. Soldiers with hay fever will be more prone to develop asthma than they would as civilians and should have specific therapy. These patients should also be evaluated on the basis of their willingness to do duty. Their ability to adapt themselves to their disability should be determined. The value to the Army of a soldier with mild or moderate asthma should be considered in relation to his type of training. These patients are infinitely better adapted to an inside job of a clerical nature than to outside duties requiring exercise. Many men with asthma for the first time while overseas have returned to duty without any specific treatment. In making this review of the first hundred cases of bronchial asthma at the Percy Jones General Hospital, the following conclusions have been reached:

SUMMARY

1. Men with active bronchial asthma should not be inducted into the Army.

2. Soldiers with bronchial asthma may be placed on nonstrenuous duty if:

(a) attacks are due to a single sensitivity for which rapid, adequate treatment is available,
(b) attacks are mild or infrequent, not preventing light duties,
(c) the initial attack was overseas, and
(d) the attack in the Army was a recurrence from childhood.

DISCUSSION

DR. F. M. RACKEMANN.—Major Alford has indeed a problem. To discuss it adequately would be to discuss the classification of asthma in all its details and this would require a long time. Suffice it to say that asthma is a symptom which has many causes. In the treatment of the disease, the progress of the patient and the chance of his recovery depend entirely upon the nature and cause of his asthma.

Last summer I made ward rounds in the hospital at Camp Edwards with Lieutenant Colonel Lewis Webb Hill. In one ward was a group of boys suffering from various obscure ailments, headaches, stomach trouble, and asthenia of various varieties, and among them were several boys with asthma. Each presented a difficult problem, and curiously not one of the boys seemed to be particularly anxious about his return to duty. The second ward contained patients with meningitis, and here the whole atmosphere was different. The sick boys were pleased to know that they were better today, and the convalescents thought only of how quickly they could leave the hospital. The contrast between the two wards was quite impressive.

Similar principles concern those boys who have been to the office and want letters for the Army. When the asthma depends upon a simple cause, ragweed, cat hair, or a feather pillow, the problem is simple; the man knows well how to deal with it; and his one idea is to get into the Army. He wants to make light of his sensitiveness, saying that he knows how to avoid trouble. He is quite correct; such a man makes a good soldier. On the other hand, the next man has a complex problem; he is sensitive to many things; the cause of his trouble is not clear-cut. He may have lesions in his nose and sinuses which complicate the picture. It is easy to see that in the Army his trouble will continue and that he should not be accepted by the Army.

The point of this is that asthma is a symptom which depends often upon a fundamental change in the individual. Unfortunately we do not know much about the "allergic state" or the "asthmatic constitution." Major Alford has stressed the importance of the family history and has shown well that those patients who have had manifestations of allergy since early childhood are the ones who become the difficult problems later. In them the allergic state is well established; they have the "capacity to develop sensitiveness to foreign substances."

Please do not think that asthma is either entirely allergic or entirely nervous. There is a clear-cut allergic group, and on the other hand there is probably a small purely nervous group, but between the two are all sorts of gradations and with complications of various kinds thrown in to make the problem difficult indeed.

I would compliment Major Alford on an interesting presentation of a timely subject.

(Proceedings to be continued.)

Original Articles

A CONSIDERATION OF SOME ALLERGY PROBLEMS

I. Allergic Dermatitis (Eczema)

Robert A. Cooke, M.D., New York, N. Y.

INTRODUCTION

WHEN Dr. Forman asked me some months ago for a title for this lecture, I suggested a very broad and noncommittal one that would permit a more leisurely consideration in the selection of certain aspects of allergy that would, I hoped, be of interest to you and that have engaged the attention of myself and my associates in recent years.

To my mind there is hardly a phase of allergy that is not still a problem—actually very little has been settled. We have some facts, but more theories, and we are by no means sure that the facts are correctly interpreted. As adjunct to the subject of clinical allergy, there are such general problems as classification, terminology, and standardization of test extracts. Certainly these are worthy of consideration, for sooner or later, we must learn to speak a like language, else allergy may suffer the fate of the Tower of Babel. And yet, all things considered, I believe that allergy is still in the awkward adolescent age. A sufficiently complete set of facts is not yet available and any organized attempt to regiment our ideas and standardize our thinking (or our extracts) would probably do more harm than good and delay the gradual development of the field to the goal of full maturity.

Work and yet more work, both clinical and research, and thought and interchange of ideas are the means by which progress will be attained, and this brings me to the mention of one problem that must concern all of us who are interested; that is the outstanding one of education and educational opportunity in the field of allergy.

This Allergy Forum organized by Dr. Forman now in its sixth successful year demonstrates the desire of physicians, many of them general practitioners, to learn how to use the concepts and tools of allergy to better advantage, not as a specialty, but in conjunction with general practice. The attendance is evidence not only of the worth of, but also of the need for such efforts wherever and whenever adequate instructors can be assembled.

I venture to state that but few members of this Forum ever received formal instruction in the fundamentals of allergy in medical school;

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yet the experiences in medical practice have indicated that at least a sound working knowledge could be put to profitable use. The need for more such forums as this is great, but this is not enough After medical school and internship as well as during that time the opportunities must be increased for superior and extensive training as well as for the short refresher courses. It is an arresting challenge to the allergists of today to provide opportunity for training of the better allergists of tomorrow. We need in the field not only practitioners who know how to use allergy with general medicine, but specialists trained for research and teaching on whom should rest the duty of the advancement and diffusion of knowledge in this important subspecialty of internal medicine.

There are two fields of exploration in allergy which have been of particular interest to me and my associates in recent years. Our studies have revealed nothing startling, conclusive, or even, I am sorry to say, of great immediate practical value. The best I can say for them is that they reveal the complications and the difficulties inherent in the whole field.

The first concerns allergic dermatitis and the other (Part II) deals with serologic and immunologic studies in the immediate wheal-reacting type of allergy which is typically exemplified by ragweed hay fever.

I. ALLERGIC DERMATITIS

This is today, I think, the number one problem child of allergy. Let me introduce the subject by a concise presentation of a few illustrative cases that were studied with a view toward an etiologic diagnosis, for this will help to clarify my discussion.

CASE REPORT

CASE 1.—M. C., male, aged 50, physician, suddenly in winter, about five years prior to his first consultation, developed an itching eruption of the face and hands. It cleared if he left home and reappeared a day or so after his return. Once, after taking a calomel pill, he had acute gastroenteritis and a general skin eruption. He dispensed his own drugs. Patch tests were positive after twenty-four hours to the drugs he handled containing mercury and salol.

CASE 2.—A. G., female, aged 39, housewife. A general itching eruption began one week before she came in for treatment. She had a history of a similar attack about six months previously. Each time she had had a "cold" and had taken certain pills. A patch test with the pill substance, supposedly acetylsalicylate, gave a positive reaction; but the patch test with pure acetylsalicylic acid was negative, while a test with methylsalicylate was positive. A year later a recurrence was found to be due to toothpaste flavored with oil of wintergreen.

CASE 3.—G. G., female, aged 38. For the past four summers prior to examination, this patient had an itching eruption of the skin about

the right eye only, which began in June and lasted until October. After avoiding summer fruits and vegetables the rash cleared in a few days. It reappeared on the third day after eating tomatoes on three separate trials. Patch tests on the extremities and trunk with all sorts of tomato preparations were negative. Fresh juice applied nightly directly to the right and left upper lids reproduced the typical lesion on the right lid only on the second day.

CASE 4.—D. W., male, aged 30, had autumnal hay fever for three years and was then treated for two years with reasonable results and no general or undue local reactions to the pollen extract. His maximum dose was 7,000 protein nitrogen units. The next year, after a lapse of treatment of nine months, he was tested intradermally with pollen extract of the usual strengths (10 – 100 – 1,000 protein nitrogen units per c.c.). He had the usual immediate local reactions as in previous years. Twenty-four hours later he had considerable edema and vesiculation about the test sites. This increased and covered the arm from shoulder to wrist and took four days to disappear. It was a dermatitis, not an angio-edema. Patch tests with regular ragweed extract and purified ragweed pollen albumen produced a local dermatitis beginning in 24 to 36 hours and lasted 5 to 6 days.

CASE 5.—A. V., female, aged 49, had a history of three attacks of acute swelling and eruption of the entire face and neck. These appeared a few days after an acute upper respiratory infection and lasted 10 to 14 days. The first attack was attributed to a "cold" remedy so no medicine was used before the last two attacks. There was found a dentigerous cyst of the edentulous upper right bicuspid area and a cyst of the right antrum. Hemolytic *Staphylococcus albus* was recovered from both operated areas. On three different occasions later, when the skin was normal, an acute dermatitis of the face and neck appeared 36 hours after injection of 0.05 c.c. of a 0.1 per cent suspension of the autogenous vaccine.

CASE 6.—N. S., female, aged 53, for nine years had a patchy eruption over the body which appeared and disappeared in various areas, but she was never wholly free. Under general and local care and with improved diet and vitamin therapy, she was almost free from acute attacks for six months. Then suddenly she had an acute general dermatitis which required hospitalization for a week. The only different food she had taken was cantaloupe. Two weeks after she had recovered from this attack, she again ate cantaloupe, and the following day had an acute general oozing eruption with abdominal cramps. Patch tests with fresh cantaloupe were done about ten days later and were positive. The intradermal test gave no immediate urticarial wheal. This is not the only offending food allergen, for there have been attacks not attributable to cantaloupe.

These illustrative cases demonstrate certain facts:

1. The allergens are extremely varied and may be nonprotein in nature.

2. The sensitized area although usually general may be strictly localized. (Case 3.)

3. The causative factor was discoverable either by the patch test or by a reproduction of the lesion at will following ingestion or injection of the allergen and was not determinable by the immediate urticarial wheal reaction of the scratch or intradermal test.

4. The clinical skin lesion was identical whether the allergen was applied from within or from without. (Case 1.)

It was never an immediate reaction.

Let me now approach the general discussion of allergic dermatitis by comments upon one skin lesion about which we know or think we know something. I refer to dermatitis venenata (poison ivy). From the work of Low,[1] and of Heinbecker,[2] of Straus,[3] and many others, it seems evident that dermatitis from ivy is due to a specific sensitization of epidermal cells resulting from prior contact. Since 75 to 80 per cent of the adults tested, largely here in the United States where the plant is abundant, have given positive reactions to ivy oil, a sensitization from casual contact must be considered to be a normal response of man or is what I have termed "physiological" allergy. Why this percentage is so high we do not know. Certainly this is not true for most of the important external contact allergens. Hence, it may depend upon the chemical structure of the ivy oil which makes it highly antigenic, or upon some peculiar property of the epithelial cells of most of the human race, or upon both of these factors. It is obvious that a familial background such as found in certain allergies plays no essential part in this. No transferable sensitizing antibodies have yet been found in the blood serum; they are purely hypothetical and are postulated as sessile cellular entities.

According to our present conceptions, which I believe are logical and sound, dermatitis venenata is an allergic reaction resulting from antigen-sensitized cell union ordinarily established through external contact. The same typical skin lesion results however, whether the antigen (oil) is taken in sufficient amounts by mouth or is administered by subcutaneous injection. In other words, contact may be established from within or from without; the lesion is the same although its distribution may be different. This fact is supported by many observations with other allergens and is especially well demonstrated in mercurial dermatitis which appears in properly sensitized persons regardless of whether mercury is applied in an ointment or taken as a calomel pill. (Case 1.)

It is unfortunate that the term contact-type dermatitis is being used to denote lesions resulting only from external contact as though the

method of contact were of any importance as a basis for separate classification.

Great attention has been paid to the dermatoses resulting from external contact because they constitute a large percentage of the compensable occupational diseases and because they are types of eczematous lesions in which an etiologic diagnosis is made by means of the "patch" test with some degree of success and frequency. About that we shall have more to say later. The question is whether contact eczema or dermatitis (I use the words synonomously and interchangeably) has an allergic basis in whole or in part. It would appear that we can exclude from the allergic possibilities, lesions caused by certain mechanical and physical agents, possibly excluding sunlight, and those organic and inorganic compounds which are primary irritants. Insofar as our knowledge of allergy goes, such agents do not stimulate cellular antibody reaction, but do give rise to skin lesions which may be classified as nonallergic contact dermatoses.

Many substances, however, such as dyes and their intermediates, oils, resins, coal tar derivatives, the chemicals used for fabrics, rubbers, soaps, cosmetics, and insecticides, the oils and resins of woods and plants as well as the products or the substances of bacteria and fungi and parasites—many such substances, I repeat, are known and proved antigens either by themselves or in hapten combinations. What can be said as to the probable allergic nature of skin lesions resulting from these contacts? The absence of antecedent family and personal history of known allergies such as hay fever, asthma, and food idiosyncrasy need not concern us here any more than in dermatitis venenata. Allergies of the immediate wheal-reacting type have, as we shall see, an entirely distinct immunologic basis and hence are not essential to an allergic hypothesis for these dermatoses. What, to my mind, is highly significant from an allergic viewpoint is the fact that the number of affected workers is so small. In the twelve most likely industries as given by Schwartz and Tulipan,[4] it was only 1.2 per cent of 117,000 employees. In our own clinic at the Roosevelt Hospital one patient, a florist, is sensitive clinically and by patch test to the oil of chrysanthemum, but not to the oil of tulip; whereas, another is clinically and by test sensitive to both. These men know literally hundreds of florists whose contact with these plants is as great or greater than theirs and yet produces no dermatitis. Reasoning by analogy, it does not seem to me unjustifiable or far-fetched to assume that such abnormal and infrequent reactions in otherwise normal persons are based upon a specific sensitization of the epidermis; in other words allergy. Remembering always that it is only an assumption, it makes a satisfactory working basis for research.

Many other factors are mentioned as influencing the development of contact dermatitis. They are race, age, season, sex, skin texture, dura-

tion, and extent of exposure prior to the lesion, and associated or concurrent infections. These, it seems to me, are only modifying factors which we cannot explain, for we do not know much of the pathogenesis of any type of allergy. We really cannot even be sure that prior contact is necessary.

It is certain that an hereditary background of allergy does not render a person an easy victim of sensitization to any and all substances with which contact is established. As I put it years ago,[5] "It must be assumed there are factors that predetermine the allergen for any particular case and factors determining what the clinical expression of the allergy shall be," and I must add, the age at which the sensitization shall be clinically expressed. "The average individual has contacts with hundreds of possible allergens. That in one case it should be mustard instead of milk, or cottonseed instead of dog dander (or paraphenylendiamine instead of nickel) is inexplicable; all we can say at this time is that if contact be necessary to the development of an allergy, a very slight one may suffice to set off a variable and self-perpetuating mechanism of reaction to an allergen that is predetermined by nature or inheritance, for other contacts great and small are ineffective."

To sum up this part of the discussion on so-called contact-type dermatitis, it seems to me that there are no valid objections to this now generally accepted concept of allergy in explanation of the majority of dermatoses resulting from external contact whether these be occupational, domiciliary, casual, or continual, regardless of the family and personal history of other allergies of the wheal-reacting type. As I have stated, exception must be made for those lesions caused by mechanical, physical, and primary irritants which may be classified as nonallergic.

Greater question exists with regard to that group of dermatoses exemplified by infantile eczema and neurodermatitis. The confusion arises from the paucity of our knowledge. Rarely is a causal agent found and more rarely proved. The cases, especially those of infants, are intricately bound up with the wheal-reacting types of allergy such as asthma and hay fever both as to antecedent and personal history. In our earliest studies of allergy, it was noted that almost 50 per cent of the cases of asthma of childhood gave a history of previous or existing eczema, and approximately the same proportion of cases of infantile eczema developed asthma or allergic coryza by the tenth year of age. Such association could not be overlooked. Antecedent allergy and allergy of the skin-reacting type in the patient are the reasons why the term atopic dermatitis was adopted. I regard this term as unfortunate, for the word atopy is used by some to emphasize the hereditary feature, as the word was originally meant; by others to indicate the existence of and the etiologic significance of the wheal-reacting type of allergy; and by many interchangeably as though the two were synonymous. And particularly is the term "atopic dermatitis" inappropriate as it has

come to imply that skin testing for immediate wheal reactions is a diagnostic procedure in eczema of the infantile type, which, as I shall show, it is not.

Let me now review some of the studies which Dr. Hampton, Dr. Wing, Dr. Boker, and I have made at our clinic on eczema in infancy and early childhood.

In one group of 60 odd cases, in which passive transfer tests only were done, about one-half gave positive and usually multiple reactions to inhalants and foods, while the other half gave no reaction; and yet there was no difference in the clinical picture or the course of the eczema in these two groups. The other group was small; only twenty-seven cases have been satisfactorily observed under hospital care, but each case required a great deal of time and patience. Fifteen of them had other accepted clinical allergies, such as asthma, hay fever, or vasomotor rhinitis. Seventeen cases gave positive immediate wheal reactions to one or many foods on passive transfer test. Thirteen of these were verified by direct test. If any case gave a positive transfer test to any food, that food was used if it could be eaten at all, abundantly and continuously in the diet at a time when the skin lesion was quiescent. Usually no observable reaction occurred, but in nine cases the clinical reaction to a food giving the positive immediate wheal test, by direct or indirect (passive transfer) test, expressed itself promptly, within an hour, as urticaria, asthma, or vomiting. Never yet have we observed an exacerbation of eczema from the ingestion of that foodstuff which gave an immediate wheal reaction. In many of the cases, inhalant antigens, pollens, danders, and dusts also gave positive immediate wheal reactions on test. These could be excluded readily as causes of an eczema.

Now what does this mean? The immediate positive intradermal or scratch test is an edematous wheal reaction. Proper contact with an antigen in patients so reacting and clinically sensitive results likewise in an immediate clinical reaction of the same edema type. This is an inherent property of such reactions and must be so. The eczematous reaction, as exhibited by the positive patch test or when reproduced clinically, is a delayed 24- to 48-hour reaction. It is a superficial exudative lesion of the epidermis, not a wheal. As long ago as 1932, I wrote[6] "It must be borne in mind that with the tests we should seek to duplicate (reproduce) the essential (histologic or physical) characteristics of the clinical reaction. Lack of regard for this principle has flooded medical literature with a mass of misinformation." It is promising to note that this concept is now slowly being recognized in some of the more recent publications.[7]

This is a far cry from the desired etiologic diagnosis, but a proper appreciation of the immunologic basis of the two types of allergy is essential, and is, I hope, a preliminary step to an etiologic diagnosis in infantile eczema. It is my feeling, supported by clinical observation,

that those skin-sensitizing antibodies of the wheal reaction circulating in the blood of eczematous infants are a portent of things to come in the way of future asthma and hay fever; they do not necessarily indicate any existing clinical sensitivity and never an eczematous one.

Immunologically speaking then, eczema is one thing; hay fever and all such immediate wheal-reacting allergies are another. They may and do exist side by side in the same person, and their frequent association, especially in infants and children, cannot be explained. Both are allergies, but only in the sense that they are the expression of specific antigen-antibody reactions, for pathologically and immunologically they have no known points in common.

And further, it is my opinion that external contact-type dermatitis as exemplified by dermatitis venenata and eczema not due to external contact, frequently called atopic dermatitis or neurodermatitis, are immunologically and therefore basically one and the same, and subject to diagnosis by the same procedure—namely, the patch test.

The separation of these two conditions, eczema and contact dermatitis, into distinct groups is based not upon any pathologic or known immunologic differences of the cutaneous lesion, but largely upon clinical distribution and patch test evidence that the excitant is an external contactant. When no external excitant is found, the diagnosis of eczema is made; or if chronic, neurodermatitis; and if there is a history of some such disorder as strawberry rash in the mother, then the diagnosis is an atopic dermatitis. This is not sound reasoning, and it seems to me more valid to recognize the immunologic and pathologic identity of eczema and contact-type dermatitis and stop stressing such unimportant factors as distribution and method of contact. One might just as rightly separate pollen hay fever from egg urticaria which we do not do, because both are examples of an identical immunologic reaction.

What now can be said about a determination of the specific causes of infantile and related eczema? There are two present diagnostic approaches, clinical test by trial and error and the patch test. I will admit at once that we have had little success, especially in infants. Clinical observation is tedious, and patch testing is difficult for many reasons. From our studies thus far, foods and bacterial infections seem to be the commoner agents, while external contactants may occasionally be the factor.

If these things are so, and I am satisfied that they are, then we are justified in certain conclusions:

1. Neurodermatitis of older children and adults is only chronic eczema, and should be so called.

2. Contact-type eczematous dermatitis is an allergy. Eczema of adults, children, and infants, the so-called atopic dermatitis, is also an allergy. The two are immunologically identical.

3. The method by which contact is established is inconsequential, whether it be external or internal. The type of substance, whether protein, oil, resin, or complex organic chemical (so long as it be not a primary irritant) is immaterial also.

4. Patch tests and clinical test by exposure to the antigen are the only methods available today for etiologic diagnosis.

5. Since sensitization of the skin is not always general, care must be taken to apply the patch to an area that has been the site of a lesion.

6. Intradermal or scratch tests must be discarded as diagnostic procedures in eczema, and the terms atopic dermatitis and neurodermatitis should be eliminated from our nomenclature.

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A CONSIDERATION OF SOME ALLERGY PROBLEMS

II. Serologic Studies of the Skin-Reacting Allergies (Hay Fever Type)

Robert A. Cooke, M.D., New York, N. Y.

LET us now turn to our studies of another problem in the field of allergy. This concerns itself with the serologic and immunologic aspects of the immediate wheal-reacting type of allergy, so well illustrated by hay fever.

It was the discovery of the immediate urticarial skin reaction and the appreciation of its significance as a diagnostic procedure that were in the main responsible for the development of clinical allergy together with the fact that the injection of antigen produced a degree of clinical immunity. The decade from 1910 to 1920 was largely devoted to the discovery of important skin-reacting antigens and to improvements in the technique of treatment, chiefly of hay fever, based upon empirical methods. In 1921, Prausnitz and Küstner[1] gave us a more tangible basis by the demonstration of the skin-sensitizing antibody in the blood of these allergic patients.

We will all, I am sure, agree that even today we understand little of the basic facts, and that there are many problems still to be solved. The positive skin test itself is not a criterion of clinical sensitiveness, and the results of treatment leave much to be desired. There are still too many problem cases: those that do not respond to injection and those in whom systemic reactions frequently recur.

For the past ten years I, with one or several of my associates, particularly Drs. Barnard, Sherman, Hampton, Loveless, and Stull, have tried to find out through serologic and immunologic studies certain facts that would help in the solution of the problems and that might ultimately be of practical value. We have not succeeded to any great extent, but at least we have had an interesting and often an exciting time. I hoped it might interest you if I related some of these findings some of which, but not all, have already been published.

The natural allergies of man, such as hay fever, are a spontaneous development of reactivity to substances with which we have normal natural contact. They have never yet been produced by artificial and even excessive external or parenteral contact. I am not affirming or denying that the mechanism of sensitization does or does not arise *de novo* from forces that we know not of and from other than the ordinary immunologic ones. The question will be raised, but unfortunately not settled.

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Hitherto unpublished paper by Cooke and Sherman presented at the meeting of The Society of American Bacteriologists, New Haven, Connecticut, Dec. 30, 1939.

In our studies[2] we have made use of the phenomenon of passive transfer of sensitiveness in two ways. Serial dilutions of sensitizing serum are injected into sites in the skin of normal test subjects. These sites are tested 48 hours later with antigen. This we speak of as the "dilution test" to determine the amount and probably also the activity of the skin-sensitizing antibody in the serum. One-tenth of a milliliter of diluted serum is injected in each site and tested with the allergen 48 hours later. Some sera diluted several thousand times can still give positive reactions. The second procedure is the neutralization test in which sensitive serum is mixed with graduated amounts of antigen and the mixtures are injected as sites in normal test subjects. Forty-eight hours later these sites are retested with the antigen to determine whether the antibody has been used up in whole or in part by the antigen in the mixtures.

Using these simple procedures for eliciting facts, let us first consider the skin-sensitizing antibody that circulates in the blood, and later we will discuss the so-called blocking antibody as I originally named it.[2]

A. SKIN-SENSITIZING ANTIBODY

It is a common thing to find patients giving multiple reactions. Are these due to one or to many different antibodies, each reacting with its own antigen? Table I shows the results in a case (Wol.) giving 22 positive reactions on passive transfer to biologically related and unrelated antigens. It also shows that the ragweed extract neutralizes the antibody to all but two antigens, namely plantain and sorrel. In other words ragweed was a "dominant" antigen, as we have termed it, with two exceptions in a patient with clinical hay fever from plantain, sorrel, and ragweed. The patient was treated with ragweed only. It has long been known that the amount of serum antibody was often increased after antigen[2-4] injections, and Sherman[5] showed that this was especially true in the early stages of treatment.

Table II shows that the amount of antibody for ragweed as determined by the dilution test was increased fourfold in this same patient (from 1 to 1000 before treatment to 1 to 4000 after treatment). But it is of interest to note that the antibody for plantain which was a second dominant antigen was also increased roughly fourfold from 1 to 500 to 1 to 2000.

This one of many such observations makes it seem probable that there is but one basic antibody unit so to speak, but with at least two prosthetic groups, one reacting with ragweed and those antigens it neutralized and another reacting with plantain. This is very different from multiple artificial sensitization with production of precipitins in the animal as shown in Table III, rearranged from data published by Hektoen and Boor.[6] Here there is no loss of specificity, although there are occasional divergent or extra-specific reactions. Each antigen was

responsible for its own special and independent antibody. Table IV, using the serum of the same patient (Wol.) and similarly arranged, illustrates the striking contrast between the specificity of artificial multiple sensitization and the lack of it in that derived spontaneously or naturally in man.

TABLE I

COMPOSITE TABLE SHOWING NEUTRALIZATION BY RAGWEED EXTRACT OF VARIOUS ALLERGENS THAT REACT WITH AN ANTESERUM (WOL.) IN PASSIVE TRANSFER SITES

SITES	TESTED WITH	REACTION IN SERUM-RAGWEED SITES*	REACTION IN SERUM-SALINE SITES†
1.	Low Ragweed Pollen	0	++++
2.	Marsh Elder Pollen	0	+++
3.	Mugwort Pollen	±	++
4.	Cocklebur Pollen	0	+++
5.	Plantain Pollen	++	++++
6.	Sorrel Pollen	++	+++
7.	Timothy Pollen	0	+++
8.	Orchard Grass Pollen	0	+
9.	Ash Pollen	0	+++
10.	Birch Pollen	±	++
11.	Alder Pollen	0	+++
12.	Elm Pollen	0	++
13.	Hickory Pollen	0	++
14.	Poplar Pollen	0	+
15.	Sweet Gum Pollen	0	++
16.	Pyrethrum	0	++
17.	Orris	0	++
18.	Alternaria	0	+
19.	Lycopodium	0	+
20.	Cottonseed	0	+
21.	Flaxseed	0	++
22.	Kapok Seed	0	++

*One-tenth c.c. of a mixture of equal parts of Wol. antetreatment serum and low ragweed extract (100 protein nitrogen units per c.c.) was injected into the skin of a normal test subject in each of 22 sites and tested 48 hours later with 1/40 c.c. of each of the 22 allergens. (1000 protein nitrogen units per c.c.) Reactions were recorded after 15 minutes.

†As controls, 1/10 c.c. of a mixture of equal parts of Wol. antetreatment serum and saline was similarly injected into the skin in each of 22 other sites and tested 48 hours later with the same 22 allergens. Reactions were recorded after 15 minutes.

TABLE II

DILUTION TESTS WITH WOL. SERUM TAKEN BEFORE (A) AND AFTER (P) RAGWEED INJECTIONS*

DILUTIONS	REACTION ON TEST WITH	
	LOW RAGWEED	PLANTAIN
SERUM A (6-13-39)		
1-500	++	+
1-1000	±	0
1-2000	0	0
1-4000	0	0
SERUM P (8-23-39)		
1-500	+++	++
1-1000	++	+
1-2000	+	±
1-4000	±	0

*The sites with serum A and serum P were made by the injection of 1/10 c.c. of serum and saline in the dilutions stated into the skin of a normal test subject and tested 48 hours later with 1/40 c.c. of ragweed or plantain pollen extract, each 1000 protein nitrogen units per c.c.

TABLE III

REARRANGED FROM HEKTOEN AND BOOR

SERUM ADSORBED WITH	SERUM TESTED FOR PRECIPITINS WITH												
	BEEF HGB.	CAT HGB.	DOG HGB.	HOG HGB.	HORSE HGB.	HUMAN HGB.	SHEEP HGB.	TURKEY HGB.	CHICKEN S. ALB.	CHICKEN OVALB.	BENCE-JONES	HOGAN PROT.	HORSE GLOB.
Beef Hgb.	0	±	±	±	±	±	0	+	+	+	+	+	+
Cat Hgb.	+	0	+	+	+	+	+	+	+	+	+	+	+
Dog Hgb.	+	±	0	+	+	±	0	+	+	+	+	+	+
Hog Hgb.	+	+	0	0	+	0	+	+	+	+	+	+	+
Horse Hgb.	+	+	+	+	0	+	+	+	+	+	+	+	+
Human Hgb.	+	+	+	+	+	0	+	+	+	+	+	+	+
Sheep Hgb.	+	+	+	+	+	+	0	+	+	+	+	+	+
Turkey Hgb.	+	+	+	+	+	+	+	0	+	+	+	+	+
Chicken S. Alb.	+	+	+	+	+	+	+	+	0	+	+	+	+
Ovalbumin	+	+	+	+	+	+	+	+	+	0	+	+	+
Bence-Jones	+	+	+	+	+	+	+	+	+	+	0	+	+
Hogan Prot.	+	+	+	+	+	+	+	+	+	+	+	0	+
Horse Glob.	+	+	+	+	+	+	+	+	+	+	+	+	0
Control	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +

TABLE IV

A COMPOSITE OF PASSIVE TRANSFER STUDIES SHOWING CROSS NEUTRALIZATION REACTIONS WITH ANTETREATMENT SERUM (WOL.)*

SERUM MIXED WITH	SERUM TESTED WITH									
	L. RAG.	SORREL	PLANT.	COCKLE.	OAK	HICK.	BIRCH	POPLAR	ASH	TIM.
Low Ragweed	0	+	+	0	0	0	0	0	0	0
Sorrel	+++	0	±	+	±	0	0	0	0	0
Plantain	+++	++	++	++	++	±	±	0	±	0
Cocklebur	++	++	++	0	++	+	+	±	0	0
Oak	+++	++	++	+	±	+	0	+	0	0
Hickory	+++	++	+++	+	++	±	0	±	±	0
Birch	+++	++	+++	++	+++	++	+	+	++	+
Poplar	+++	++	+++	++	++	++	++	+	++	+
Ash	+++	++	+++	++	++	+	+	+	+	+
Timothy	+++	++	+++	++	+++	++	+	±	++	±
Control	++++	++++	++++	+++	+++	++	++	+	++	+
Dilution titer	±3000	±3000	+1000	+1000	±1000	±1000	±1000	±300	+100	+100

*This table is arranged in the order of the dilution titer; that is, the reactivity as determined previously by passive transfer tests with the same allergens in serum sites of various dilutions.

This serum diluted 3000 times still gave slight reactions with extracts of low ragweed and sorrel, whereas with ash and timothy extracts no reaction was obtained after 100 fold dilutions.

Sherman and Stull[7] showed a few years ago how clinical sensitivity was related to this so-called dominance of antigen. In a patient clinically sensitive to dog dander but reacting by test to both dog and horse dander, the antibodies to both were neutralized by dog but not by horse extract. In a contrasting case of a patient clinically sensitive to horse dander but reacting by test to dog and horse dander, the horse extract neutralized both antibodies and the dog extract did not. In a third case of a patient clinically sensitive to dog and horse dander, the dog extract neutralized to itself only on passive transfer and the horse to itself and there was no cross neutralization. So you see, this question of dominance of antigen seems to carry a definite clinical significance. However, an antigen is dominant only in reference to a special serum and is definitely related to clinical sensitiveness of the patient from whom the serum is obtained, but no antigen is inherently dominant nor is there any constant relation between antigens.

One further point and we shall be done with the discussion of the skin-sensitizing antibody. We are accustomed to think of hay fever and hay fever sensitization as an entity. We shall see. Let us compare the sera of four typical hay fever patients as to their reactions and neutralizations to several related pollens. A study of Table V shows no two of these four sera completely alike. From our experiences, of which these are examples, the antibody in any particular serum when studied in detail with regard to reactions and neutralizations has what approaches a fingerprint individuality, a fact quite contrary to the general conception. This fact plus the evident lack of specificity of the skin-sensitizing antibody is at variance with the specific results usually obtained, as for example, in the work of Hektoen and Boor,[6] in studies on artificially induced antibodies. This permits us to question the classical concept of the immunologically induced origin of the skin-sensitizing antibody in the naturally sensitive man. We have grounds that permit us to raise the question, but we cannot provide a full answer.

B. THE BLOCKING OR INHIBITING ANTIBODY

Beginning as long ago as 1931, Dr. Barnard and I[2] became interested in the whys and wherefores of the apparent immunity induced in hay fever patients by proper pollen injections. For four years we carried out transfusions from treated to untreated patients at the height of their hay fever. The results, sometimes striking, indicated to us the probable presence of a transferable protective substance which we then sought to demonstrate if possible by serologic studies, again using the method of passive transfer. Serum was taken from patients before and after treatment for comparison.

The dilution test was used to indicate any quantitative alteration of the sensitizing antibody; that is, whether it was increased or decreased. Actually it was found that it was not strikingly altered; sometimes it

TABLE V

THE INDIVIDUALITY OF THE REACTIONS OF SERA FROM TYPICAL RAGWEED HAY FEVER PATIENTS

PASSIVE TRANSFER SITES*		REACTIONS OF SITES TESTED WITH THE FOLLOWING EXTRACTS†							
SERUM	MIXED WITH	LOW RAGWEED	AMARANTH	CHENOPOD	COCKLEBUR	IVA	MUGWORT	SAGE	RUSSIAN THISTLE
Hre.	Saline	++++	++	++	+++	++++	+++		++
Hre.	L.R. 1000 U.	0	0	0	0	0	0		0
Aar.	Saline	++	++	+++	+++	+++	++		++
Aar.	L.R. 1000 U.	0	+	+++	+	+	+		+
Wilk.	Saline	+++	++	++	++	++	+++	+++	
Wilk.	L.R. 1000 U.	++	0	0	±	+	++	++	
Elaz.	Saline	++++	+	±	+	+++	0	0	
Elaz.	L.R. 1000 U.	0	0	0	0	0	0	0	

*The various sera, Hre., Aar., etc., were mixed in equal parts with saline or low ragweed (1000 protein nitrogen units per c.c.), and 1/10 c.c. of each such mixture was injected into the skin of normal test subjects to create sites for later testing.

†Forty-eight hours after sites were made, they were tested by the injection of 1/40 c.c. of each of the various extracts into various sites as shown.

Note: If one compares both the passive transfer test (serum and saline) and the neutralization test (serum and ragweed), it will be observed that no two of these sample sera behave exactly alike.

was increased especially in the early stages as mentioned, but usually diminished somewhat after long and intensive specific treatment. The neutralization test with allergen-antibody mixtures, however, showed a significant alteration. When sites were made there was an immediate wheal reaction, if untreated serum was used in the allergen-serum mixture, but none or slight reaction if serum of treated cases was used. When the sites previously made with these mixtures were retested with antigen alone after 48 hours, reactions were absent or slight with antetreatment serum, but positive when posttreatment serum was used. This is well illustrated in Table VI. It was our conclusion from these studies that under treatment a new antibody was present in posttreatment serum which blocked or inhibited the reaction in the first place, leaving the antibody in the cell to react at the later 48-hour test. These observations have been amply confirmed.

TABLE VI

COMPARISON OF ANTETREATMENT AND POSTTREATMENT SERUM (BUSCH) TEST SUBJECT, D.L.

DILUTION TESTS		NEUTRALIZATION TESTS			
DILUTIONS* ANTETREATMENT	REACTION TO TEST†	MIXTURES MADE WITH EQUAL AMOUNTS OF‡		REACTION OF SITES	
		BUSCH SERUM	RAGWEED UNITS PER C.C.	1 HR. AFTER SITES WERE MADE	ON RETEST§
1-10	+++				
1-100	++	Antetreatment	50	+++	0
1-200	++	Antetreatment	100	+++	0
1-300	+	Antetreatment	150	+++	0
1-500	±	Antetreatment	Saline	0	++++
Posttreatment		Posttreatment	150	0	++
1-10	++	Posttreatment	300	0	++
1-100	++	Posttreatment	500	0	++
1-200	+	Posttreatment	700	0	++
1-300	0	Posttreatment	1000	±	+
1-500	0	Posttreatment	Saline	0	+++

*One-tenth c.c. of the stipulated dilutions of serum in physiologic saline was injected into each site.

†The serum dilution sites were tested 48 hours later with 1/40 c.c. low ragweed extract, 100 protein nitrogen units per c.c.

‡One-tenth c.c. of these serum-ragweed or serum-saline mixtures was injected into each site.

§The serum-ragweed or serum-saline mixture sites were tested 48 hours later with 1/40 c.c. low ragweed, 100 protein nitrogen units per c.c.

Further studies[8] on this unusual antibody have shown some very interesting points. It may be produced in normal persons by the injection of the antigen without giving rise to any skin-sensitizing antibody.

Dr. Loveless,[12] after extensive and painstaking work, believes, if I sensitizing antibody which is destroyed by heat. Sherman, Hampton, and I[10] found that it readily permeated placental membrane and was found in cord blood, whereas it had been shown by Bell and Eriksson[11] and confirmed by us that the sensitizing antibody was not transmitted from mother to fetus.

Further, it was shown that this antibody binds antigen, although it does not form a definite precipitate except possibly with special technique, and finally this antibody has a very strict specificity in line with all artificially induced antibodies, as exemplified by the experiments of Hektoen and Boor, already quoted. This is quite in contrast with the lack of specificness of the skin-sensitizing antibody about which I have already spoken. This is well illustrated in Table IX.

TABLE VII

THE DEVELOPMENT OF BLOCKING (INHIBITING) ANTIBODY IN A NORMAL PERSON (J.)*

SKIN SITE ON TEST SUBJECT	SERUM-RAGWEED MIXTURES FOR SITES†		REACTION AT SITE WHEN TESTED AFTER 48 HRS. WITH RAGWEED EXTRACT‡
	SERUM COMBINATIONS	RAGWEED UNITS PER C.C.	
1	J. serum A + H serum (ragweed sensitive)	50	++
2	J. serum A + H serum (ragweed sensitive)	100	+
3	J. serum A + H serum (ragweed sensitive)	200	0
4	J. serum A + H serum (ragweed sensitive)	Saline	+++
5	J. serum P + H serum (ragweed sensitive)	200	+++
6	J. serum P + H serum (ragweed sensitive)	300	++
7	J. serum P + H serum (ragweed sensitive)	400	++
8	J. serum P + H serum (ragweed sensitive)	600	+
9	J. serum P + H serum (ragweed sensitive)	800	±
10	J. serum P + H serum (ragweed sensitive)	1000	0
11	J. serum P + H serum (ragweed sensitive)	Saline	+++
	Controls		
12	B serum + H serum (ragweed sensitive)	50	++
13	B serum + H serum (ragweed sensitive)	100	+
14	B serum + H serum (ragweed sensitive)	200	0
15	B serum + H serum (ragweed sensitive)	Saline	+++
16	Saline + H serum (ragweed sensitive)	50	+
17	Saline + H serum (ragweed sensitive)	100	+
18	Saline + H serum (ragweed sensitive)	200	0
19	Saline + H serum (ragweed sensitive)	Saline	+++

By permission of J. Exper. Med. 66: 694, 1937.

*J. serum A was taken from a nonallergic person before injections of ragweed pollen extract. J. serum P was taken after a course of injections of ragweed pollen extract. As it did not transfer, it had to be mixed with a sensitizing serum H. Normal serum B and saline were used as controls. It took 6 to 8 times as much ragweed to neutralize J. serum P as J. serum A.

†These mixtures consisted of one part of serum combination (sensitizing and non-sensitizing serum in equal parts) and one part of ragweed extract of designated strength. One-tenth c.c. of the serum-ragweed or serum-saline mixture was used for creating each passive transfer site in the skin of a normal test subject.

‡One-fortieth c.c. of low ragweed extract (1000 protein nitrogen units per c.c.) was injected into each site.

The fact, then, is that injections of pollen extract have been shown to produce a special immune body, or rather bodies, for there may be one that is specific for each of the protein fractions in the pollen extract. This, then, is the story of the blocking antibody, which after all is really of the nature of precipitin rather like the soluble precipitins of Pappenheimer, Heidelberger, and others.

I have spoken of it as an immune body, but I mean this only in the sense that it was produced as the result of an immunologic procedure; that is, pollen protein injections (ragweed extract). The question is:

TABLE VIII

THE TRANSMISSION OF THE BLOCKING ANTIBODY THROUGH THE PLACENTA AS SHOWN BY THE INACTIVATION OF RAGWEED EXTRACT BY POSTTREATMENT HEATED SERA (CORD AND MATERNAL)*

DILUTIONS OF SERA (HEATED) PLUS L.R.	REACTION OF PASSIVE TRANSFER SITES PREPARED WITH LOW RAGWEED SENSITIVE SERUM (Rr. 1-10) AND TESTED 48 HOURS LATER WITH:					
	GHL. CORD SERUM + L.R.	GHL. MATERNAL SERUM + L.R.	ARO. CORD SERUM + L.R.	ARO. MATERNAL SERUM + L.R.	BED. CORD SERUM + L.R. (CONTROL)	BED. MATERNAL SERUM + L.R. (CONTROL)
Concentrated	0	0	0	0	++	++
1-3	0	0	0	0	++	++
1-9	0	0	0	0	++	++
1-27	0	0	0	0	++	++
1-81	0	0	0	0	+	+
1-243	0	0	0	0	0	0

*In this experiment six rows of six sites each were made on the back of a normal test subject by injecting 1/10 c.c. of a ragweed-sensitizing serum (Rr. 1-10 dilution) in each site for testing 48 hours later. The cord and maternal sera were heated at 56 degrees centigrade for four hours to destroy the skin-sensitizing antibody. To each serum was added an equal amount of low ragweed extract (10 protein nitrogen units per c.c.) and allowed to stand overnight. No precipitate was observed. For the later testing we injected 1/40 c.c. of these serum-ragweed mixtures concentrated and in the dilutions shown.

The results show that even in the concentrated mixtures the ragweed extract was inactivated by the posttreatment maternal and cord sera, whereas in the controls a positive reaction was obtained down to a 1:81 dilution. The blocking antibody from the material serum had passed through the placenta to the fetal blood.

By permission of J. Exper. Med. 72: 616, 1940.

TABLE IX

STRICT SPECIFICITY OF INDUCED BLOCKING ANTIBODY IN A RAGWEED-TREATED PATIENT*

DILUTIONS OF SERA (HEATED) PLUS POLLENS	REACTION OF PASSIVE TRANSFER SITES PREPARED WITH RAGWEED SENSITIVE SERUM (SCR. 1-10) AND TESTED 48 HOURS LATER WITH:					
	DTCH. P-SERUM + LOW RAGWEED	DTCH. P-SERUM + COCKLEBUR	DTCH. P-SERUM + MUGWORT	WTSN. SERUM + LOW RAGWEED (CONTROL)	WTSN. SERUM + COCKLEBUR (CONTROL)	WTSN. SERUM + MUGWORT (CONTROL)
Concentrated	0	++	+	++	++	+
1-3	0	++	±	+	++	+
1-9	0	+	±	±	+	+
1-27	0	±	0	0	±	0
1-81	0	0	0	0	0	0

*The technique in this experiment is the same as that described for Table VIII. Dtch. P-Serum is a heated posttreatment ragweed-reacting serum, and Wtsn. Serum, as control, is a heated antetreatment ragweed-sensitizing serum.

This experiment shows that the antibody developed by injections of ragweed extract inactivated ragweed extract only and not cocklebur or mugwort extracts, although the patient Dtch. reacts to these extracts, and more significant yet, in other passive transfer tests, ragweed extract neutralized the skin-sensitizing antibody for both of these extracts as well as ragweed.

TABLE X

THE EFFECTS OF RAGWEED POLLEN INJECTIONS ON PATIENTS SENSITIVE TO CERTAIN FRACTIONS OF RAGWEED POLLEN

CASE	REACTION OF PASSIVE TRANSFER SITES TESTED WITH: FRACTION 1	FRACTION 2	NEUTRALIZING ANTIBODY DEVELOPED FOR: FRACTION 1	FRACTION 2	HIGHEST DOSE*	CONSTITUTIONAL REACTIONS	CLINICAL IMPROVEMENT
1	++	0	+	0	6000	0	90%
2	++	0	+	0	2000	0	Marked
3	++	0	+	0	1500	0	80%
4	++	0	+	0	8000	0	95%
5	++	0	+	0	5500	0	75%
6	++	0	+	0	10,000	0	50%
					Av. 5300		
7	++	±	+	0	1000	1	90%
8	++	+	+	0	2000	2	75%
9	++	+	+	0	700	1	Marked
10	++	+	+	0	1250	0	Fair
11	++	++	+	0	2000	2	90%
12	++	++	+	0	1250	0	75%
					Av. 1360		
13	++	++	+	+	7500	0	98%

*Protein Nitrogen Units per c.c.

Is it really *the* immune body responsible for the clinical protection afforded certain treated hay fever patients?

Dr. Loveless,[12] after extensive and painstaking work, believes, if I understand her correctly, that at least in large part it is. The weakness of this contention as I see it lies in these facts. Her studies were made with whole ragweed extracts, that is, protein mixtures and not with the separate purified proteins. We know from the work of Hecht et al,[13] of Stull et al.,[14] and of Rockwell[15] that there are several protein fractions in the pollen. The usual inhibiting antibody is to the albumen fraction 1 rather than the proteose fraction 2, which also is definitely and clinically important. This question cannot be finally decided until serologic studies are carried out using purified fractions of pollens. Further, she postulates from her results that the amount of this immune body must be many fold greater for some patients than for others. The orthodox conception of a protective antibody is that a certain amount would protect against a certain amount of antigen. There is no basis for thus individualizing the protective behavior of a protective antibody; that is, contending that it varies for the patient rather than for the amount of antigen. Further, if one can reason by analogy, a very justifiable procedure, precipitation, or rather agglutination which is its counterpart, has never yet been shown to relate itself to clinical immunity in bacterial disease.

However, I do not believe this blocking antibody is devoid of all effect, although I am not yet convinced that it is the important factor in clinical immunity. I feel I must introduce some evidence of a glimmer of a practical result from all this work.

Table X shows that Ragweed Hay Fever Cases 1 to 6 reactive only to fraction 1 and with blocking antibody for fraction 1 only took average doses of over 5000 protein nitrogen units of ragweed extract without systemic reactions from the injections, whereas Cases 7 to 12 reacting to fraction 1 and fraction 2, but with antibody only to fraction 1, were able to take doses averaging less than 1500 units, and with a total of six general reactions. Case 13, reactive to and with antibody to both fractions, took doses up to 7500 units with no reaction. In other words, the presence of this antibody seems to permit increased dosage without the danger of the constitutional reaction. Table XI

TABLE XI

SKIN REACTION TO FRACTION 2 (100 PROTEIN NITROGEN UNITS PER C.C.) IN RELATION TO INCIDENCE OF CONSTITUTIONAL REACTIONS IN CERTAIN RAGWEED HAY FEVER PATIENTS

INTRACUTANEOUS TESTS	TOTAL CASES	CASES HAVING CONSTITUTIONAL REACTIONS	PERCENTAGE OF CASES HAVING CONSTITUTIONAL REACTIONS
Slight-negative	79	10	13
Moderate	64	34	53
Marked	71	62	87

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from Sherman and Hebald's[16] paper shows that patients very sensitive to fraction 2 do not tolerate large doses of ragweed well, and the intradermal test with the proteose substance called fraction 2 by Stull will help in advance to determine those problem cases that are apt to have constitutional reactions and should be treated with special caution.

Further work both chemical and serologic has been interrupted by the war. This is just as true with everyone else as with our group. Let us hope that the time is not too far distant when we may all resume our studies in security and in confidence in a world at peace.

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THE VOLUMETRIC INCIDENCE OF ATMOSPHERIC ALLERGENS

II. Simultaneous Measurements by Volumetric and Gravity Slide Methods. Results With Ragweed Pollen and Alternaria Spores

Oren C. Durham, Chicago, Ill.

IN A PREVIOUS paper[1] I assumed a conservative attitude toward the tables worked out by Scheppegrell[10] and Cocke[2, 3] which show rates of fall for pollen grains and give factors for converting gravity slide pollen figures into volumetric equivalents. I also called attention to the surprising lack of experimental data on the subject. Later Dahl and Ellis,[4] after a futile attempt to apply these factors,[5] disapproved the Scheppegrell-Cocke theoretical volumetric method because of "the fact that data concerning specific gravity and velocity of fall of pollen grains, of both smooth and echinate types, are at present inadequate." Such data are still inadequate even though in the first paper of the present series[6] I have established approximate specific gravity figures for several kinds of common air-borne pollens.

If our 20-year accumulation of gravity slide figures for pollen and fungus spore incidence has any statistical meaning at all, it is high time that we establish their volumetric significance. To do this it will be necessary to subject the gravity sampling method, as well as the proposed method for its volumetric interpretation, to rigid experimental test. This paper presents some evidence bearing on both of these phases of the problem.

In reporting his experiments on the rate of fall in still air of fungus spores of *Amanitopsis vaginata*, 10 microns in diameter, Buller[7] concluded that "for the present it would seem as though the spore fall method of testing Stokes' Law shows that the actual velocity of fall of spheres about 10 microns in diameter is some 50 per cent greater than the law demands." Likewise in Dyakowska's[8] experiments on "the falling down of the pollen of some trees" and similar work by several other European investigators,[9] the reported rates of fall have been, in almost every case, greater than that allowed by the Scheppegrell-Cocke-Dahl[4] tables based on Stokes' law, the increase in some cases amounting to considerably more than 100 per cent. None of these experiments was carried out for the purpose of determining the volumetric incidence of air-borne particles in outdoor air, but they strongly suggest the need of some adequate technique for checking the accuracy of any theoretical conversion factors derived from Stokes' law.

VOLUMETRIC TESTS BY COCKE AND HAWES

The first effort to evaluate the Scheppegrell-Cocke tables was that of Cocke,[3] who, at University, Va., in 1937, operated a simple volumetric

From the Biological Laboratories of Abbott Laboratories.

pollen trap simultaneously with a gravity slide. His precipitating device had a capacity of about 2 cubic feet of air per hour. By comparing the number of pollen grains of a given species found on 1 square centimeter of the gravity slide (on a 24-hour exposure basis) with the number of pollen granules of the same species recovered from a cubic yard of air, he satisfied himself that the theoretical figures derived from Stokes' law are reasonably accurate. But since Cocke's volumetric apparatus caught 32 per cent more ragweed pollen grains per cubic yard of air than the number predicted from the gravity catch, it seemed reasonable to him to agree with Scheppegrell's[10] suggestion that ragweed pollen spicules cause an appreciable slowing effect on the rate of fall of ragweed pollen. However, since Cocke was unaware of the low specific gravity of ragweed pollen and had not included this factor in his formula for computing the ragweed content of the air, his actual ragweed volumetric catch, instead of being 32.2 per cent more than should have been expected, was actually 23 per cent less than the revised calculation allows. If account were also taken of the assumed slowing effect of the ragweed spicules, the discrepancy would, of course, have been considerably more than 23 per cent. Thus, in this experiment, if we assume that both the gravity and volumetric data were dependable, we must conclude that the ragweed pollen grains failed to obey Stokes' law in that they fell too fast, just as the tree pollens did for Dyakowska and the fungus spores for Buller. It would, however, be just as logical to attribute the discrepancy to inaccuracies in sampling either by the gravity test or by the volumetric device.

More recently Hawes (with co-workers)[11] has reported from Los Angeles a comparative gravity volumetric study similar to that of Cocke, in which he used a volumetric impinger apparatus which sampled approximately 5 cubic feet of air per hour. The only kind of pollen tested by both Cocke and Hawes was that of "grass." Cocke recovered 19 per cent less grass pollen than the theoretical figure predicted by the Scheppegrell-Cocke factors and suggested that this difference might be caused by a possible specific gravity for grass pollen greater than 1. Hawes' discrepancy for grass pollen was of the same order and amounted to 31 per cent. Since it has been shown[6] that the specific gravity of grass pollen must be very close to 1, it seems from these two experiments that grass pollen also falls faster than the formula allows. Indeed, all but one of the other five kinds of pollen tested by Hawes showed similar discrepancies, giving rates of fall varying from 12 per cent to 59 per cent faster than the rates predicted by Scheppegrell-Cocke-Dahl factors.

Unfortunately, southern California did not afford air-borne pollens of any kind in sufficient quantity for a statistical verification of the accuracy of the Scheppegrell-Cocke-Dahl figures. In a continuous 26-day study, Hawes' average daily pollen catch (with the exception of one species of pollen on one windy day) was less than 2 pollen grains per species per cubic yard of air, and for any given species on the gravity

slides about ⅓ of a pollen grain per square centimeter per day. Moreover, of the six species of pollens studied by Hawes, only one is spherical in shape when dry enough to float in the air, so any data derived from the five irregularly shaped pollens are unsuitable for drawing definite conclusions regarding the accuracy of figures based on the Stokes formula. Nevertheless, while he called attention to possible grave inaccuracies of the gravity sampling method, Hawes concluded: "It is confirmed that the Scheppegrell-Cocke formula for calculating pollen concentration from the results of gravity slide experiments is approximately correct."

APPARATUS AND TECHNIQUE FOR VOLUMETRIC TESTS

The volumetric sampling device which had been used by Hawes and described in his report was placed at my disposal for parallel gravity volumetric experiments and has been used during the ragweed seasons of 1942 and 1943 in Illinois. The location chosen for carrying out the air sampling was the flat roof, 182 × 165 feet, of a warehouse at Abbott Laboratories in North Chicago, Ill. This building was higher than any surrounding building (55 feet above ground) with the roof unobstructed except for two small penthouses.

Simultaneous gravity slide exposures and volumetric runs with the Hawes device were made thirty-nine times during the late summer and fall of 1942 and eight times during August, 1943. The gravity slides were coated with a very thin film of vaseline, no label being used, and were exposed face up on the end of a vertical 22-inch rod (as suggested by Hawes[11]) placed several feet from the volumetric apparatus.

Early in the 1942 season it was found that for no apparent cause the ratio between the gravity and volumetric catch of ragweed pollen from day to day varied enormously. In order to learn the source of these erratic results it was decided to set up a second volumetric apparatus of entirely different design as a control on the first, and to operate both devices simultaneously with a gravity slide. The control device finally adopted for the 1943 experiments was similar to that used by Keitt and Jones[12] in their studies on the atmospheric incidence of apple scab spores. It consists essentially of a vacuum pump which pulls air through a nitrocellulose filter at the rate of about 60 cubic feet per hour. An ordinary gas meter was connected in series between the filter and the vacuum motor, and the difference in pressure between the air entering the meter and that outside was measured by a suitably connected manometer. The attenuation was calculated at 10 per cent, and corrections were made accordingly before tabulating the results shown in an accompanying table.

At the end of each run the nitrocellulose filter plug bearing the pollen grains, fungus spores, and other aerial debris was placed in a 150 c.c. beaker and dissolved in about 50 c.c. of a liquid composed of three parts, by volume, of ether to one of absolute alcohol. One drop of

saturated aqueous solution of fuchsin was added. Stirring was continued while evaporation proceeded until the resulting liquid approached a syrupy consistency. Several samples were then poured on clean glass slides where evaporation was completed. The resulting film of collodion containing the stained pollen grains was less than 20 microns in thickness. The film usually adhered perfectly to the slides and allowed convenient counting of all pollen grains and fungus spores under the microscope. By careful weighing of the films and of the residue in the beaker after thorough evaporation, it was possible to determine the weight of the collodion on the counted slides as compared with that of the total batch. The pollen and fungus spore count for several different slides was found to vary directly with the weight of the collodion film on each slide. The total catch was thus calculated from a known proportion.

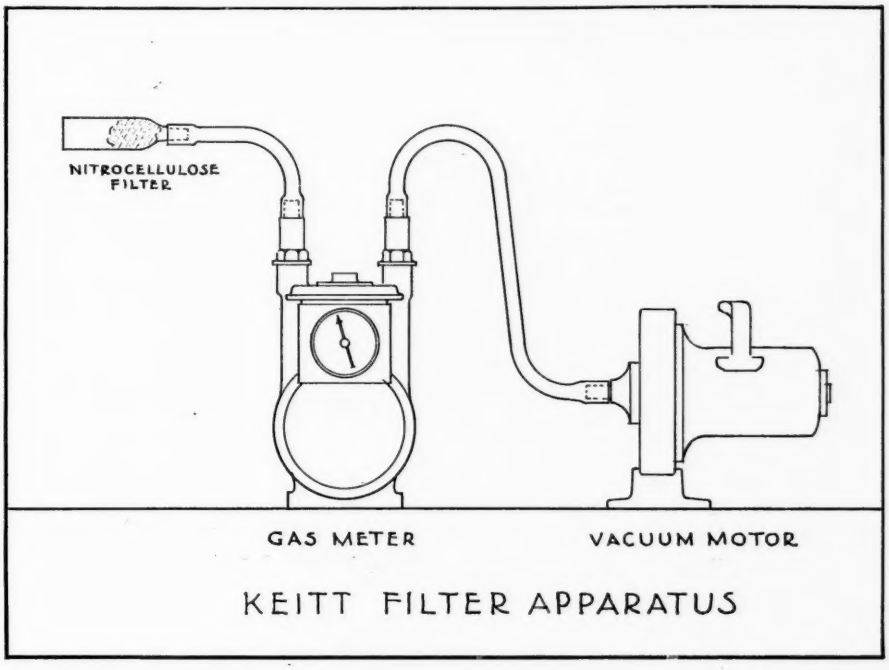

Fig. 1.

Tables I and II show that no run was continued for as long as 24 hours, the average length being about 7 hours. But regardless of the volume of air sampled during a given run, the volumetric catch was calculated and recorded in the number of particles per cubic yard of air. Also in counting the gravity slides for these runs it was necessary to count a proportionately larger area, for example, 3 square centimeters for an 8-hour run, so that the resulting figure would represent the equivalent catch of a 24-hour gravity slide exposure. When the amount of pollen on the gravity slide was small, it was often found advisable to count the whole surface of the slide in order to get an average figure

TABLE I

COMPARATIVE VOLUMETRIC STUDY, 1942. HAWES IMPINGER COMPARED WITH GRAVITY SLIDE

DATE	PREVAILING WIND DIRECTION	AVERAGE VELOCITY PER HR.	TOTAL TIME OF EXPOSURE HR. MIN.	RAGWEED			ALTERNARIA			RATIO OF RAGWEED TO ALTERNARIA (B/A)
				GRAVITY, NO. PER 1 SQ. CM.	IMPINGER, NO. PER CU. YD.	(A) RATIO	GRAVITY, NO. PER 1 SQ. CM.	IMPINGER, NO. PER CU. YD.	(B) RATIO	
7/31/42	W	8	7 40				73	919	12.6	
8/ 2/42	WNW	6	3 45				3	84	28.0	
8/ 3/42	W & NW	10	45				15	244	16.2	
8/ 4/42	NE	4	7 48				3	85	28.3	
8/ 5/42	E	5	8 30				1.3	36	28.1	
8/ 6/42	SE	6	4				3	61	20.2	
8/ 7/42	SE & E	6	5 45	2	6.7	3.4	3.8	45	11.8	3.5
8/10/42	NW	6	6				15	107	7.1	
8/11/42	N	12.5	8 25	4	7.4	1.9	1.4	28	20.2	10.8
8/12/42	NW & E	6.25	8 05	0.7	6.3	9.0	0.7	20	29.1	3.2
8/13/42	E & SE	5.4	8 40	2	9.7	4.9	0.7	132	188.5	38.8
8/14/42	SW	13	8 25	22	40	1.8	7	285	40.7	22.1
8/15/42	W	11.3	5 15	22	139	6.3	6.6	263	39.8	6.3
8/17/42	W	8	7 40	52	102	2.0	10.5	136	13.0	6.6
8/18/42	W & SW	15	8 15	46	141	3.1	9	185	20.6	6.7
8/19/42	SW	12.3	16	34	61	1.3	3.2	115	35.7	19.8
8/20/42	SW	14.5	7	56	129	2.3	24	470	19.6	8.5
8/24/42	S	9.6	6 30	16	89	5.6	0	11.5	78.4	13.6
8/24/42	S	9.4	16 15	16	95	5.9	0.24	12	78.4	13.6
8/25/42	S	15.3	7 35	140	346	2.5	4.5	31	6.8	2.8
8/25/42	SE	7.3	16 50	29	532	18.3	2	44	22.2	1.2
8/26/42	S	9.5	2 15	152	1120	7.4	0	88	40.8	6.0
8/26/42	S	12	5 30	83	516	6.2	2	49	40.8	6.0
8/27/42	SW	11.5	8 30	122	605	5.0	2	77	38.6	7.8
8/30/42	SE	8	3 40	147	991	6.7	13	520	40.0	5.9
8/31/42	SW & SE	7.5	8 40	108	956	8.8	22	715	32.6	3.7
9/ 1/42	SW	14	4	155	857	5.5	20	639	32.0	5.8
9/ 3/42	N & NE	15.6	8 20	22	148	6.7	1.4	56	40.3	6.0
9/ 4/42	NW & SE	9	7 12	5	90	18.0	0	87	69.4	5.0
9/10/42	W	5	7	12	117	9.8	0	66	69.4	5.0
9/11/42	SW & SE	10.8	6	13	108	8.3	5.71	221	69.4	5.0
9/13/42	SW & SE	6.7	6	31	274	8.8	2	240	119.8	13.6
9/14/42	SW	14	8	54	211	3.9	10	280	28.0	7.2
9/15/42	S	18	4 55	81	151	1.9	44	478	10.9	5.8
9/16/42	SW	13	8 25	29	57	2.0	26	431	16.6	8.4
9/17/42	SW	11.5	7 55	8	20	2.5	2.5	95	38.1	15.3
9/18/42	S	18.3	7 45	19	56	3.0	10	380	38.0	12.9
9/21/42	S	13.7	6	2.4	15	6.3	5.7	128	22.4	3.6
9/22/42	W & N	10.6	6 25	1.3	17	12.7	0.9	38	41.9	3.3
Totals			285 40	1486.4	8013.1		354.14	7900.5		
Averages		10.1	7 20							
Ratios of totals						5.39			22.31	4.14

Averages	10.1	7	26							
Ratios of totals						5.39			22.31	4.14

TABLE II

COMPARATIVE VOLUMETRIC STUDIES, 1943

DATE	PREVAILING WIND DIRECTION	AVERAGE VELOCITY PER HR.	TOTAL TIME OF EXPOSURE HR.	RAGWEED			ALTERNARIA			RATIO OF RAGWEED TO ALTERNARIA (B/A)
				GRAVITY, NO. PER 1 SQ. CM.	VOLUMETRIC, NO. PER CU. YD.	(A) RATIO	GRAVITY, NO. PER 1 SQ. CM.	VOLUMETRIC, NO. PER CU. YD.	(B) RATIO	
A. Hawes Impinger Compared With Gravity Slide										
8/15/43	S	8	5	8	167	20.9	8	243	30.4	1.5
8/17/43	N	10	8	3	80	26.7	2	78	39.0	1.5
8/18/43	NW	6	6	6	146	24.3	1	133	133.0	5.5
8/25/43	W & E	6	8	323	2547	7.9	8	223	27.9	3.5
8/27/43	NE	16	6	42	370	8.8	0.3	67	223.3	25.3
8/29/43	SW	8	5	175	776	4.4	12	306	25.5	5.8
8/30/43	SW & SE	7	6	127	1140	9.0	4	238	59.5	6.6
8/31/43	S	8	8	371	1512	4.1	27	702	26.0	6.3
Totals			52	1055	6738		62.3	1990		
Averages		8.6	7.5							
Ratios of totals						6.39			31.93	5.00
B. Keitt Filter Compared With Gravity Slide										
8/15/43	S	8	5	8	119	14.9	8	92	11.5	0.8
8/17/43	N	10	8	3	59	19.7	2	44	22.0	1.1
8/18/43	NW	6	6	6	130	21.7	1	42	42.0	1.9
8/25/43	W & E	6	8	323	2425	7.5	8	121	15.1	2.0
8/27/43	NE	16	6	42	297	7.1	0.3	67	223.3	31.6
8/29/43	SW	8	5	175	1158	6.6	12	256	21.3	3.2
8/30/43	SW & SE	7	6	127	1082	8.5	4	163	40.7	4.8
8/31/43	S	8	8	371	1809	4.9	27	949	31.4	6.4
Totals			52	1055	7079		62.3	1734		
Averages		8.6	7.5							
Ratios of totals						6.71			27.83	4.15
Average ratio of totals by both methods, 1943						6.55			29.88	4.57
Average ratio of totals by impinger, 1942						5.39			22.31	4.14
Average ratio of totals for 1942 and 1943						5.97			26.08	4.37
Theoretical ratio when corrected for specific gravity						12.69				

Theoretical rate of fall. Ragweed pollen .022 ft. per sec. (20 microns) (corrected).
Experimental rate of fall. Ragweed pollen .048 ft, per sec. (20 microns).
Experimental rate of fall. Alternaria spores .011 ft, per sec.

that would have some statistical value. Even then it was apparent that most of the larger discrepancies in the ratio between gravity and volumetric catches were on days when the atmospheric pollen or spore content was low. It should also be noticed from the tables that these large discrepancies have little weight in the final averages because the latter were calculated from seasonal totals of the gravity catch and volumetric catch respectively.

SOURCES OF ERROR

Several possible sources of error are apparent in the techniques of testing and calculation used in this study. Among them are:

1. Variable size of air-borne particles. This factor is of little importance in experiments with ragweed pollen granules because of their remarkably uniform size throughout the season. Daily measurement of the average diameter of a representative number of ragweed pollen grains established this point and set the figure at 20 microns. Alternaria spores are extremely variable in size. Hence it was to be expected that there would be some lack of uniformity in their behavior as compared with that of the ragweed granules.

2. Convection currents, deflection currents, and wind eddies. These must interfere with a horizontal flow of air and hence with the deposit of pollens and spores on the gravity slide. There seems to be no way of calculating the magnitude of these disturbing factors.

3. Clumps of pollen. Aggregates of any size, even as few as two or three granules, must certainly fall at a rate totally different from that of a single granule. Clumps of 20 to 50 granules of pollen are sometimes encountered on gravity slides when tests are made in too close proximity to weeds. The presence of large clumps can introduce enormous errors into theoretical volumetric calculations. In this study only a very few aggregates, either of pollens or fungi, and these small ones, were encountered.

4. Efficiency of volumetric devices. Careful tests showed that the free air in the Hawes impinger was at all times almost 100 per cent free from pollen grains and other particles. The filter device was proved to recover more than 95 per cent of the pollen in the air passing through it.

STANDARDS

Assuming that the determination of .55 as a specific gravity for short ragweed pollen grains of 20 microns diameter[6] applies to all of the ragweed pollens caught by all methods during these tests, and omitting any possible reduction in speed of fall because of the spicules of the pollen, the theoretical (Stokes' law formula) rate of fall of the ragweed pollen grains encountered in the course of this study should be 0.022 feet per second. If this rate of fall had operated constantly without interfering vertical wind currents, the number of ragweed pollen grains

caught in either of the two volumetric devices per cubic yard of air should have been on every run not less than 12.7* times the amount found on 1 square centimeter of gravity slide (24-hour basis). No standard rate of fall or conversion factor could be set up for Alternaria spores because of their decidedly irregular shape and greatly variable size.

DISCUSSION OF RESULTS

The most striking finding in the course of these experiments is the utter inconsistency of the daily ratios between gravity and volumetric figures. Instead of a constant gravity catch of approximately $\frac{1}{13}$ of the volumetric amount, the catch was sometimes more than one-half of the volumetric recovery, or seven times as much as the theoretical figure—a 700 per cent error! On a few days the gravity catch was quite low and only once did the proportion agree with theory. These tremendous differences in the comparative catch by the volumetric and gravity devices have not been mentioned by Cocke and were noted only on one day by Hawes.

Proof that most if not all of these discrepancies are chargeable to inaccuracies of the gravity sampling method is found in the remarkable agreement of the results from the two volumetric devices, both for ragweed pollen and for fungus spores. In the ragweed tests the maximum divergence from the mean volumetric reading on any one day was only 20 per cent and the average divergence less than 3 per cent.

The tables show that in general, though not invariably, the proportionate catch of pollen on the gravity slides varied directly with the wind velocity. Since the largest excess amounts on the gravity slides tend to occur with the higher wind velocities, it seems reasonable to conclude that strong winds not only interfere with an even horizontal flow of air, but frequently act as an impinging force. To test this point, several slides were exposed in various positions in a 22-mile per hour wind. One was placed in the normal gravity slide position, another tipped at an angle of 45° to the wind, the third vertical facing the wind, the fourth slide tipped at an angle of 45° with the oil face downward, and the fifth slide faced directly downward. The vertical and diagonal slides caught five to ten times as much ragweed pollen as the horizontal gravity slide, and the inverted horizontal slide actually caught 50 per cent as much as the normal gravity slide. It is thus evident that in strong winds there are upward as well as downward currents and that impingement can, under such conditions, be responsible for more of the "gravity" catch than is gravity.

In the light of this simple experiment it is not surprising to find that in the volumetric studies the gravity slides caught on the average one-sixth as many ragweed granules per square centimeter as the volumetric

*Number per cubic yard $= \frac{6.97 \times \text{number per sq. cm.}}{\text{rate of fall} \times 24}$ (see references 4 and 6.)

devices recovered per cubic yard of air, whereas the average ratio, according to the Stokes law formula, should have been about 1 to 13. Thus the gravity slides caught more than twice as much pollen as predicted. A theoretical rate of fall calculated from these findings comes out as 0.049 feet per second instead of 0.022 feet per second, but obviously the figure has no practical significance.

It has already been shown that Cocke caught more ragweed pollen on his gravity slide than the corrected theoretical figures allow. However, his discrepancy was not quite so great as that just noted. It is entirely possible that the wind velocities during the short time of his experiment were considerably less than they averaged during the time of my experiments. It seems necessary to repeat here the criticism that the figures given by Cocke for his ragweed test are evidently based on the content of considerably less than 2 cubic yards of air either in one straight 12-hour test or the average of several tests which he did not enumerate specifically.

Finally, the day by day ratios between the gravity catch and volumetric recovery of Alternaria spores was found to be even more variable than the ragweed ratios. Moreover, there was less agreement between the two sets of ratios than might have been expected. However, it is evident that whatever the nature of the factors causing these greater inconsistencies in the Alternaria gravity catch, they had comparatively little disturbing effect on the daily Alternaria recovery by the two volumetric devices. Indeed, the agreement of the volumetric data on both ragweed and Alternaria by the two devices is the most satisfactory outcome of this effort.

SUMMARY

1. In obtaining representative samples of the pollen and fungus spore content of the air under the best conditions I could provide, two volumetric devices of totally different design, one of which sampled more than ten times as much air as the other, recovered practically the same number of pollen grains and Alternaria spores per cubic yard of air on a given day. Simultaneously exposed gravity slides caught amounts of pollen and spores varying greatly day by day in comparison to the amounts gathered by the volumetric apparatus.

2. In forty-seven tests over a total period of 337 hours, the average excess of the gravity catch of ragweed pollen over the theoretical standard was more than 100 per cent.

3. The greatest excess catch of ragweed on gravity slides usually occurred on days of highest wind velocity, but the degree of this inaccuracy could not be predicted with any certainty.

4. Rates of fall for various types of pollen grains cannot be calculated from the rate of deposit of air-borne pollen on outdoor gravity slides because of the unavoidable impinging effect of frequent descending wind currents. Therefore the Scheppegrell-Cocke-Dahl tables are

of no practical value in converting gravity slide figures to accurate volumetric equivalents.

5. This study shows that over a long period of time, under the special conditions described in this paper, and with average wind velocities of about 10 miles per hour, the average ragweed pollen catch on a gravity slide (1 sq. cm., 24 hours) is approximately one-sixth of the average number of ragweed pollen grains in 1 cubic yard of air. If subsequent experiments in other places with comparable wind velocity should show an average similar proportion, it may be possible to use the following arbitrary conversion factors: 5.97 when the unit area counted on the gravity slide is 1 sq. cm., 3.2 when the unit area is 1.8 sq. cm.

6. Under the conditions enumerated above the average catch of Alternaria spores on a gravity slide (1 sq. cm., 24 hours) is $\frac{1}{26}$ as much as the actual average Alternaria spore content per cubic yard of air. If subsequent experiments in other places with comparable wind velocity should show an average similar proportion, it may be possible to use the following arbitrary conversion factors: 26.08 when the unit area counted on the gravity slide is 1 sq. cm., 14.5 when the unit area is 1.8 sq. cm.

7. Since no simple volumetric device is yet available for routine atmospheric tests, it may be necessary for some time to continue to rely on gravity slides, but they must be regarded henceforth as being much more inaccurate than many workers have assumed. It is possible that the gravity sampling method can be improved.

8. For volumetric testing the Hawes device is to be recommended for accuracy and simplicity.

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CLINICAL EVALUATION OF ASCORBIC ACID IN THE TREATMENT OF HAY FEVER

SELIAN HEBALD, M.D.
NEW YORK, N. Y.

VITAMIN C has been shown to be a relatively simple chemical substance closely allied to hexuronic acid. It has been appropriately named ascorbic acid ($C_6H_8O_6$), and is also referred to as cevitamic acid.

Ascorbic acid was isolated by Szent-Györgyi during 1928, from oranges, lemons, and cabbages; and from the suprarenal cortex. It has a high reducing power, is soluble in water and alcohol, and is readily destroyed by heat and oxidative processes.

The essential function of Vitamin C appears to be the maintenance, in a normal state, of the intercellular ground substance in which the tissue cells are embedded and cemented together. The manner in which it exerts its effect is unknown. There is ample evidence that it serves as a hydrogen transporter in the respiratory enzyme system of plant cells, but evidence of its playing a corresponding role in animal tissues is inconclusive. The respiratory activity of scorbutic tissues is not reduced nor does an increase in oxygen consumption result from the addition of ascorbic acid to such tissues.

With the new developments in the knowledge of vitamins has come a flood of reports dealing with the relationship of Vitamin C to various forms of hypersensitiveness. On few aspects of the subject has there been any uniformity of opinion. Frequently, different investigators have arrived at diametrically opposite conclusions. We are here concerned only with an evaluation of the clinical results of feeding Vitamin C during the hay fever season to patients having ragweed hay fever in New York City; that is, patients having clinical hay fever from Aug. 15 to Oct. 1.

Holmes and Alexander* have reported on the clinical effect of feeding varying amounts of Vitamin C to twenty-five patients having ragweed hay fever. They found that before treatment the daily Vitamin C excretion in the urine of twelve patients averaged only 10 mg., indicating a very low level. (The daily average Vitamin C excretion in the urine of a healthy individual of average weight is from 30 to 50 mg.) They also found that their best clinical results were obtained when each patient received 500 mg. of Vitamin C daily. With this dosage, eight patients reported remarkable clinical improvement after three or four days, and there was a distinct over-all clinical gain in 88 per cent of their twenty-five patients.

From the Roosevelt Hospital, Department of Allergy.
*Science 96: No. 2500.

TABLE I

EVALUATION OF ASCORBIC ACID TREATMENT

PATIENT	REACTIONS TO TEST WITH RAGWEED EXT.	DURATION OF HAY FEVER	DATE VIT. C. STARTED IN 1943	SYMPTOMS AFTER 1 WK. OF 500 MG. VIT. C., DAILY	LENGTH OF TIME VIT. C. WAS TAKEN AND NET CLINICAL RESULT
1. Coe No. H. E. Female, Aged 24	Moderate, marked	3 yrs.	8/27/43 No previous treatment	Bad hay fever	4 wks. Bad result, more hay fever during 1943 than 1942. Last seen 9/24/43
2. Win No. 7966 Female, Aged 38	Moderate	20 yrs.	8/17/43 Treated 6 yrs. through 1942	Bad hay fever	4 wks. Bad result, 4 wks. of severe hay fever. Last seen 9/27/43
3. Mit No. 6532 Female, Aged 24	Marked	14 yrs.	8/24/43 Treated 1940 and 1941	Bad hay fever	3 wks. Much hay fever throughout. Last seen 9/17/43
4. Lev No. 7971 Female, Aged 36	Marked	6 yrs.	8/27/43 No previous treatment	Bad hay fever	4 wks. Same amount of hay fever as during 1942. Last seen 9/24/43
5. Rei No. 7972 Female, Aged 24	Marked	3 yrs.	8/27/43 No previous treatment 6 wks. pregn.	Bad hay fever	4 wks. Same amount of hay fever as during 1942. Last seen 9/24/43
6. Bar No. 7969 Female, Aged 29	Moderate	3 yrs.	8/24/43 No previous treatment	Bad hay fever	3 wks. 17 days bad hay fever. Whole result better than 1942. Last seen 9/28/43
7. Wei No. 7973 Male, Aged 33	Marked	2 yrs.	9/7/43 No previous treatment	Bad hay fever	3 wks. Worse hay fever than 1942. Last seen 9/28/43
8. Car No. 7981 Male, Aged 42	Marked	3 yrs.	9/7/43 Treated 1942	Bad hay fever	3 wks. Much hay fever 8/15 to 9/17. Better during 1942. Last seen 9/17/43
9. Hen No. 7977 Female, Aged 40	Marked	11 yrs.	9/3/43 Treated 1939 and 1940	Some hay fever	3 wks. Moderate amount hay fever all season, but better than 1942. Last seen 9/24/43
10. Sil No. 5336 Female, Aged 33	Marked	7 yrs.	8/23/43 Treated past 5 yrs., small doses ragweed in 1943	Bad hay fever	4 wks. Very bad hay fever all season, worse than 1942. Last seen 9/27/43

We selected a group of ten cases. Nine of these were new cases which we saw for the first time at the clinic and which came to us after Aug. 15. These nine received no treatment of ragweed extract during 1943. The tenth case had been treated unsuccessfully at this clinic for four years and was under preseasonal and coseasonal treatment with small doses of ragweed extract during 1943. All ten were definite unques-

tioned cases of clinical ragweed hay fever with typical symptoms between Aug. 15 and Oct. 1. All gave moderate or marked reactions on intradermal test with 0.02 c.c. of a mixture of equal parts of giant and low ragweed extract in the strength of 100 protein nitrogen units per c.c. Each patient received 500 mg. of ascorbic acid* daily, divided into two doses, 250 mg. each, one taken at about 8 A.M. and the second at about 6 P.M. All patients reported at the clinic weekly and received a small injection of alkaline saline diluting fluid at each visit, except the tenth patient who was given small doses of ragweed extract. Five patients took the ascorbic acid for a period of four weeks, and five for a period of three weeks. Blood serum and urine determinations for Vitamin C content were not done.

Table I gives a brief résumé of the ten cases. Eight had a great deal of hay fever throughout the 1943 season. In these, there seemed to be no benefit whatsoever. Two patients felt that they were somewhat improved over 1942, although each of these still had a goodly amount of hay fever.

SUMMARY

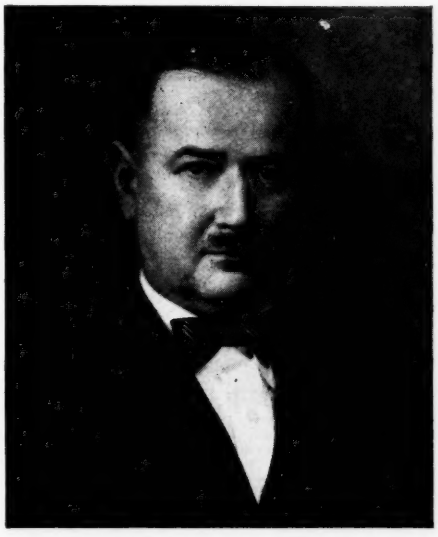
1. In a small group of cases, the uniformly poor results led to the impression that Vitamin C is not an effective form of treatment for hay fever.

2. The comparison of 1943 with 1942 seems entirely fair, since the pollen counts were practically identical in New York City during both years: 933 in 1942, and 1002 in 1943.

*Ascorbic acid used in this study was obtained through the courtesy of E. R. Squibb & Sons, New York.

WARREN TAYLOR VAUGHAN

THE tragic death of Warren Vaughan has removed a distinguished member from the company of those devoted to allergy. He was one of the pioneers. His interest in allergy began when allergy emerged as a clinical entity. He was identified with every significant development of the subject in this country. He served continuously on the Council of the American Society for the Study of Allergy, in which he held every office. He was President of the Society for the Study of Asthma and Allied Conditions in 1938, and for fourteen years was Associate Editor of THE JOURNAL OF ALLERGY. His bibliography is extensive, and his books are well known.



Those who knew him during his medical lifetime were aware of the influence of his illustrious father, who was prominent in American medicine of his day. Warren Vaughan's purpose to maintain a high tradition was apparent, and this aim he imbued in his four sons who have begun their medical careers. He interested himself in many aspects of medicine, served on several national committees, and was on the editorial boards of numerous publications.

Warren Vaughan was generous, kindly, and had the capacity for making lasting friendships. The editors of THE JOURNAL OF ALLERGY hereby record their sense of profound loss in his passing.

Editorials

Capillary Changes in Migraine

ANY light that may be shed on the mechanism of an allergic manifestation or on the basic constitution that promotes that mechanism can be of inestimable value not only to that particular syndrome but to others related. It is gratifying to note, therefore, that recent studies have been reported in connection with migraine.[1] The capillaries in the skin at the cuticle base and in the mucosa of the lower lip were observed. During the migraine attacks, impaired visibility or blurring of the capillary outlines was the most constant feature. Subsequent to the injection of ergotamine tartrate, there was a definitely increased capillary visibility. Forced water intake resulted in migraine attacks in the majority of instances in the period of water retention following the four-hour period of "excess excretion." During such periods there was an associated blurring of the capillaries. The authors conclude that there is a definite relationship between the fluid balance of the body, the state of the peripheral capillaries, and the migraine attack. They believe that the distinctness of the capillary outlines is directly related to the transudation or exchange of material through the capillary wall. Presumably, similar changes occur in the cerebral vessels.

These observations also disclosed the fact that in the majority of instances of patients with migraine there were abnormalities in capillary structure discernible in the periods between attacks. These changes constitute a tortuosity of the limbs of the capillary loop, an increase in the number of crossings, the occurrence of knobbings, and variations in diameter in the different limbs. The variability in capillary diameter described by them resembles that reported previously[2, 3] as the "angioneurotic diathesis." Recently, it has been indicated by Mueller[4] that those persons who have the above changes in capillary form and diameter tend to possess an increased susceptibility to vasomotor disturbances, allergy, and migraine. Are we approaching nearer to a solution of the understanding of the mechanism of migraine and allergy and of the constitutional basis for these conditions? The least that can be said is that such work is basic and should be pursued more diligently.

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—*S. M. F.*

Yellow Fever Vaccine and Egg Antigen

THE use of specific therapeutic or prophylactic agents such as vaccines and toxins produced on protein-containing media has continually elicited speculation and reports concerning allergic reactions from the substances in such media. In recent years the growing tendency to the employment of the living egg as a culture tube, particularly for virus and rickettsial organisms, has created another and perhaps more important phase of this allergic problem. Since egg is a highly antigenic substance, it is possible that in the preparation of the virus, sufficient egg antigen may be carried with it to produce reactions in sensitive individuals. Apparently such a case is reported[1] in a soldier who received a single dose of yellow fever vaccine. In less than five minutes following the injection, there resulted an acute reaction consisting of dyspnea, wheezing, vomiting, diarrhea, angioneurotic edema, and loss of consciousness. Following recovery, the patient gave a history of a long-standing tendency to mild attacks of asthma, and more severe attacks from feathers, chicken, and egg. Ingestion of the latter would produce, in addition, vomiting, diarrhea, and angioneurotic edema. There was also a familial history of asthma. Clinical tests with the feeding of chicken meat and egg corroborated the patient's story. Intradermal tests with egg, chicken, and yellow fever vaccine produced strong immediate whealing reactions. Reagins were shown to be present to these three antigens.

The question that naturally arises is the relationship of the vaccine preparation to the egg and chicken antigens. An attempt was made to answer this by cross-desensitization technique. Unfortunately at this point the experiments were not clear-cut. Transfer sites exhausted to egg white reacted to chicken. When the reaction to the latter had disappeared, the same sites, an hour later, were tested with the vaccine, with very slight reaction. Another series of sites desensitized to chicken and reacting to egg, was tested after an interval of one hour to the vaccine, with marked reaction. It is obvious that a number of faults in technique would tend to place doubt on the value of such experiments. The successive use of the same site for three different antigens, the short intervals between desensitizing doses, and the lack of any quantitative considerations in the antigens are among the evident criticisms. It is difficult, therefore, to see how the author comes to the interpretation of "This is conclusive evidence that the reaginic fraction of yellow fever vaccine is related both to egg white and chicken meat structurally and reaginogenically; that it more closely resembles egg white than it does chicken meat." In spite of the incompleteness of the immunologic data, one gains the impression that sensitivity to the yellow fever vaccine implies a sensitiveness to the egg or chicken or both. In anaphylactic experiments on guinea pigs with yellow fever vaccine and chick embryos it has been shown that the

older the embryo, the more closely its antigen compares with the yellow fever vaccine virus.[2]

This case, along with a similar one related to us by an Army medical officer, should cause the medical officer to be on the guard for similar instances, not only because of their immediate clinical application, but because of the exceptional opportunity this would give for the observation of basic immunologic data.

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—*S. M. F.*

Evaluation of Therapeutic Procedures

THE extreme capriciousness of behavior of clinical manifestations of allergy are only too well known to those who deal constantly with these disorders. At times we can attribute these variations to such factors as differences in concentration of pollen or differences in degree of exposure to other allergens, or to the influence of such secondary factors as weather, dust, infection, nervous tension, and endocrine disturbance. In many instances and on many occasions we must admit that we are totally ignorant of the nature of such factors influencing allergic response. To compensate for the deficiencies in our knowledge, we have learned that we must be conservative in the evaluation of therapeutic procedures. We have learned of the necessity for prolonged observation, controlled conditions, repeated experiments, objective data wherever possible, and sufficient data to be clinically significant. The average practitioner, who sees allergic patients now and then, is, of necessity, unable as a rule to evaluate treatment in this manner. He is often apt to be influenced by the temporary response of a patient or two. Frequently his impression is gained from a report published by someone who may be more hasty than discreet, or who may be an incurable therapeutic enthusiast, or at least one who is unprepared or unwilling to subject his experiments to properly controlled conditions. Not infrequently such preliminary reports are inspired or at least encouraged by commercial interests. Once launched, such therapeutic products tend to become widely employed, their interest frequently maintained by repeated favorable reports from those who prefer print to science, and those numerous medical journals who cater to quantity rather than to quality. Oftentimes it takes years—years in which sufferers receive worthless remedies, lose valuable time and needed funds—before the majority of deluded physicians and the deluded patients come to their senses. We have only to enumerate a

few of such remedies to recall to the reader not only their general lack of beneficence, but also the long periods with which they have been (and, in some cases, still are) on our horizon: cortical extracts; thyroid extract; vitamins D, C, E, B, and B complex; calcium salts; potassium salts; oral pollen; acids; "coli metabolin," sprays, masks, and nasal filters.

What remedial measures can we as allergists offer to remedy this situation? It is evident that we must publicize the idea that before acceptance of any new remedy the practitioner should learn to depend on the published evaluation of recognized experts in the field. To justify such publicity we should make greater individual and concerted effort to undertake such experimentation and to report the results promptly, whether positive or negative. In the past, in many instances, complete reports on therapeutic procedures have been tardy, oftentimes because of the hesitancy of the experimenter to report negative findings. It is evident that an organized agency for the prompt evaluation of medicaments and modalities relating to allergy would be capable of accomplishing inestimable good for the cause of allergy, the general medical profession, and the public. It is gratifying, therefore, that such a committee (Committee on Medicaments and Pharmaceuticals), appointed by the American Academy of Allergy in December, 1944, is already energetically engaged in therapeutic evaluations and other therapeutic problems.

—*S. M. F.*

Announcement

IN THIS issue of the Journal, ALLERGY ABSTRACTS makes its first appearance. This heretofore privately circulated publication has been important in that the field of allergy is widely covered (although the editors are discerning in their selections). The abstracts have always been carefully and systematically edited and most welcome to those who have been on the private mailing list.

THE JOURNAL OF ALLERGY is indeed fortunate to have the privilege of publishing ALLERGY ABSTRACTS within its covers, and acknowledgment is made to the Jewish Hospital of Brooklyn. By offering a wider circulation, the Journal will thereby fulfill an important function.

—*H. L. A.*

Book Review

Pathology and Therapy of Rheumatic Fever. L. Lichtwitz, M.D., New York, 1944, Gruene and Stratton, pp. 210, illustrated.

The author believes that rheumatic fever is not an infectious disease caused by a specific microorganism or virus, but an allergic response to various antigens, particularly bacterial products. This thesis is pursued logically in terms of clinical and pathologic findings. The allergic shock tissue in rheumatic fever is identified as the mesenchyme, and its wide distribution accounts for the disseminated lesions, especially the associated arteritis.

From this point, the author proceeds to compare the lesions of serum sickness and of periarteritis nodosa with those of rheumatic fever. Similar arterial manifestations are observed in disseminated lupus erythematosus, in some instances of Osler's syndrome of visceral disorders with cutaneous manifestations (Henoch's purpura), and in dermatomyositis. He feels that these conditions call less for differentiation than for correlation. This concept seems apropos at this time, particularly in view of the recent studies of Rich who produced typical Aschoff bodies in rabbits during the development of periarteritis nodosa following injection of horse serum.

Beyond this point, it becomes difficult to follow the maze of applications of the author's concept. However, the book provokes thought, and those interested in the broader aspects of allergy will find in it a good deal of worth-while reading.